SYNTHETIC ENTRIES INTO THE BICYCLO[2.1.1]HEXANE SYSTEM

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B.S., Southeastern State College, 1968

Submitted to the Department of Chemistry and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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To Lavada, my wife

ACKNOWLEDGMENTS

I wish to express my appreciation to Dr. R.G. Carlson for his guidance and patience that he extended to me during the years of this investigation. I want to acknowledge the relationships built with my fellow graduate students as enjoyable.

To my mother and father, who have sacrificed dearly to help me stay in school, I extend my deepest appreciation.

I gratefully acknowledge the financial support provided to me by a Berger Scholarship, Stauffer Chemical Company, and the Alfred P. Sloan Foundation.

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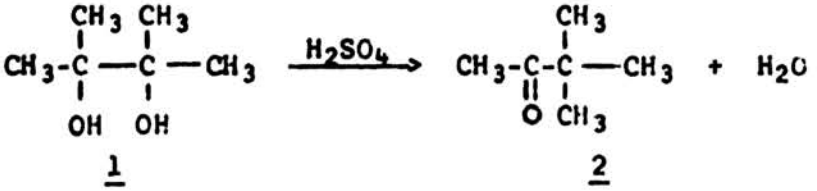
INTRODUCTION

Pinacol and Pinacol Type Rearrangements

Rearrangements in saturated systems are very common phenomena that are observed during the course of many types of reactions, such as substitution, elimination and addition. Despite the reaction type differences, the rearrangements exhibit a close family resemblance with their oldest history belonging to carbonyl-forming eliminations.[1]

In 1859 Fittig discovered pinacol (1),[2a] and in 1860[2b] he observed that when diol 1 was stirred with concentrated sulfuric acid, a new compound, pinacolone (2), was isolated from the reaction mixture. The

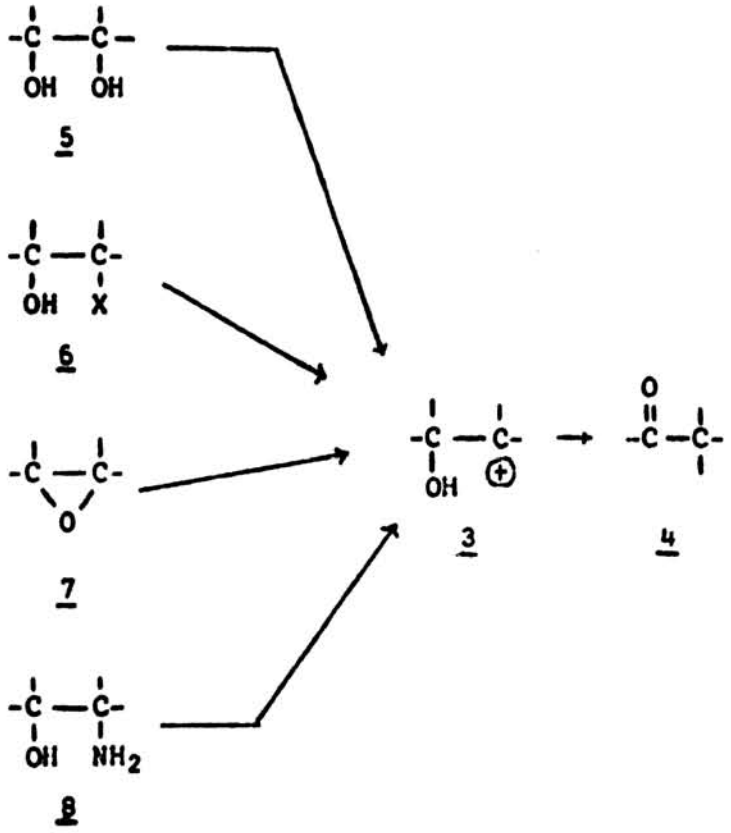


1 2

striking feature in this reaction was the migration of a methyl group from one carbon atom to another. This reaction is now known as the pinacol-pinacolone rearrangement.[3,4]

Since Fittig first observed this rearrangement, this type of transformation has been utilized extensively in the laboratory, a fact that is confirmed by a literature search. It has also been found that the starting glycol need not be di-tertiary and the migrating group need not be methyl but can be any alkyl group, aryl group, or hydrogen.[1] When the starting glycol does not have two tertiary hydroxyl groups adjacent to one-another but undergoes a similar transformation, the rearrangement is termed a semi-pinacol change,[5] a term which was initiated by Tiffeneau and Orekhoff[6] to indicate the rearrangement of a secondary-tertiary glycol to a ketone by dehydration and migration.

The accepted mechanism[4] for the pinacol rearrangement involves protonation of one of the hydroxyl groups which can either be displaced in a concerted fashion by a migrating alkyl group or ionize to give a free carbonium ion which can then undergo a 1,2-alkyl shift and deprotonation to form the carbonyl product. With the concept of the mechanism in mind, it is easily seen that any compound that contains a suitable leaving group,



which can generate an electron deficient center alpha to the carbon bearing the hydroxyl group has the potential of undergoing a semi-pinacolic rearrangement. Just a few of the many examples are the solvolyses of halohydrins 6,[7] the silver-ion catalyzed reaction of halohydrins 6,[8] the protic- and Lewis acid catalyzed ring opening of epoxides 7,[9] and the nitrous acid deamination of amino-alcohols 8.[10] In all but a few cases the corresponding glycols are not obtained, but instead, invariably

a carbonyl compound was recovered.

A variety of alternative modes for the generation of carbonium ion 3, and hence, the possibility of a semi-pinacol rearrangement, are available. For example, the treatment of certain lactones with acid, Lewis acid or protonic acid treatment of some α- hydroxy ketones, the treatment of certain allylic alcohols with N-bromosuccinimide, tert-butyl hypochlorite, or aqueous acid, anodic oxidation of β-hydroxy acids, the solvolysis of certain α-hydroxy sulfonate esters, as well as the treatment of certain cyclic olefins with thallium(III) salts generate carbonium ions similar to 3 which can then react to give rearranged products.[11]

Even though many examples of semi-pinacol rearrangements have been presented, no mention has been made as to why the reaction works. There is not a single, simple explanation because the course of just one reaction can depend upon many factors such as the solvent system used, the acid that is employed, substituent effects, conformational effects, and steric effects. In general, one might speculate that the driving force for the reaction is provided as a result of the particularly high bond strength of the carbonyl group in the product.[11]

In addition to the above rearrangements, all of which proceed via an ionic intermediate that has directed our attention towards a cationic center, there are a large number of semi-pinacol rearrangements that are initiated by a basic species, hence, the reactive intermediate is an anionic species rather than a cationic species. Even though different intermediates are involved the end result is the same, namely, the conversion of a suitably substituted compound to a reactive anionic species which then collapses to a carbonyl product by concurrent migration of one substituent with displacement of a good leaving group.

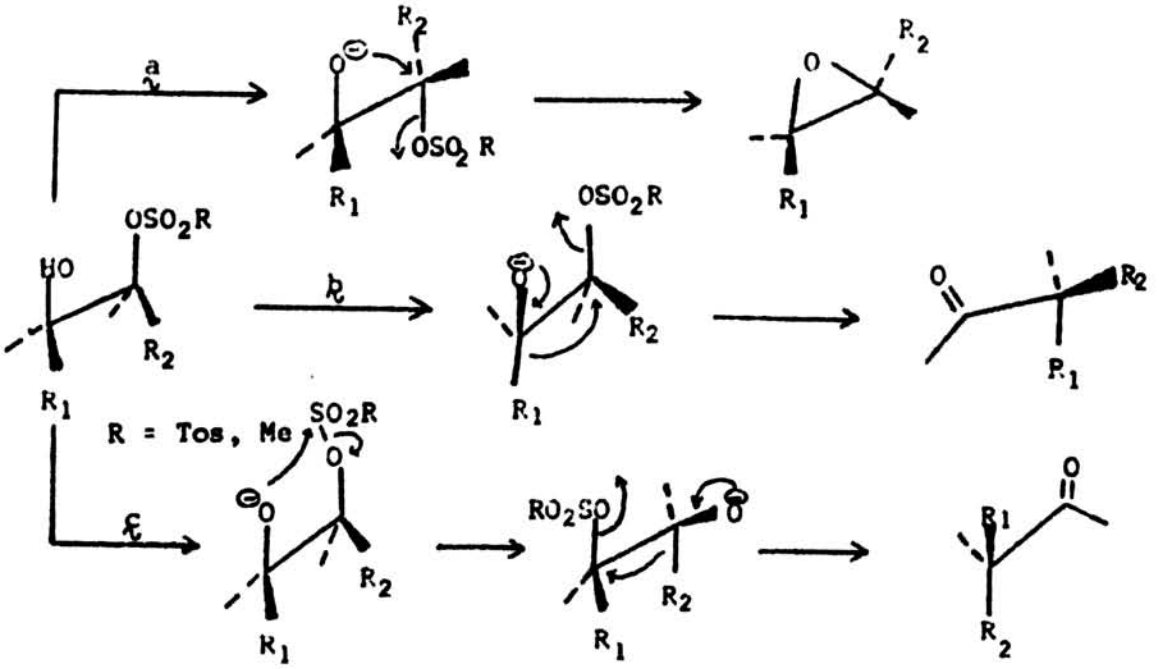
The inherent advantages of the base-induced rearrangement over the acid-catalyzed is that the reaction conditions are usually not as severe, fewer by-products are formed, higher yields are obtained, and the preservation of acid sensitive functional groups elsewhere within the molecule. The strength of the base can be quite varied with the starting material dictating whether it be the weakly basic carbonate or anything in-between and up to and including the highly basic species tert-butoxide.

Just a few of the base-induced reactions that may be viewed as a semi-pinacol rearrangement include the dehydrohalogenation of certain bromohydrins,[12] the decomposition of certain α-hydroxyalkylmercuric chlorides,[13] reaction of α-ketols with base, rearrangement of 1,2-glycol monosulfonate esters, the benzilic acid rearrangement,[11] as well as the Grignard induced rearrangement of certain α-haloketones.[14]

Owing to the nature of the work done, emphasis will be placed on the base-induced reaction of 1,2-glycol monosulfonate esters, and later, attention will be directed toward the reaction of selected bromohydrins. The reaction of the above esters with base has found great synthetic utility in the expansion[15] and contraction[16] of four-, five- and six-membered carbocyclic rings by semi-pinacol rearrangements. A brief review of this particular rearrangement will be presented so as to help explain the results that were obtained during the course of this investigation.

Compounds that contain a tertiary hydroxyl group adjacent to a secondary tosylate (or mesylate) group have the potential of undergoing reaction when treated with a base. The function of the base is to produce a reactive anion by the removal of the acidic proton from the tertiary hydroxyl group. This anionic intermediate can then react by one of three

possible pathways to displace the tosylate group. The mode of displacement of the tosylate group and thus, the products obtained, are goverened by the stereochemistry of the starting compound. Path a is simply the

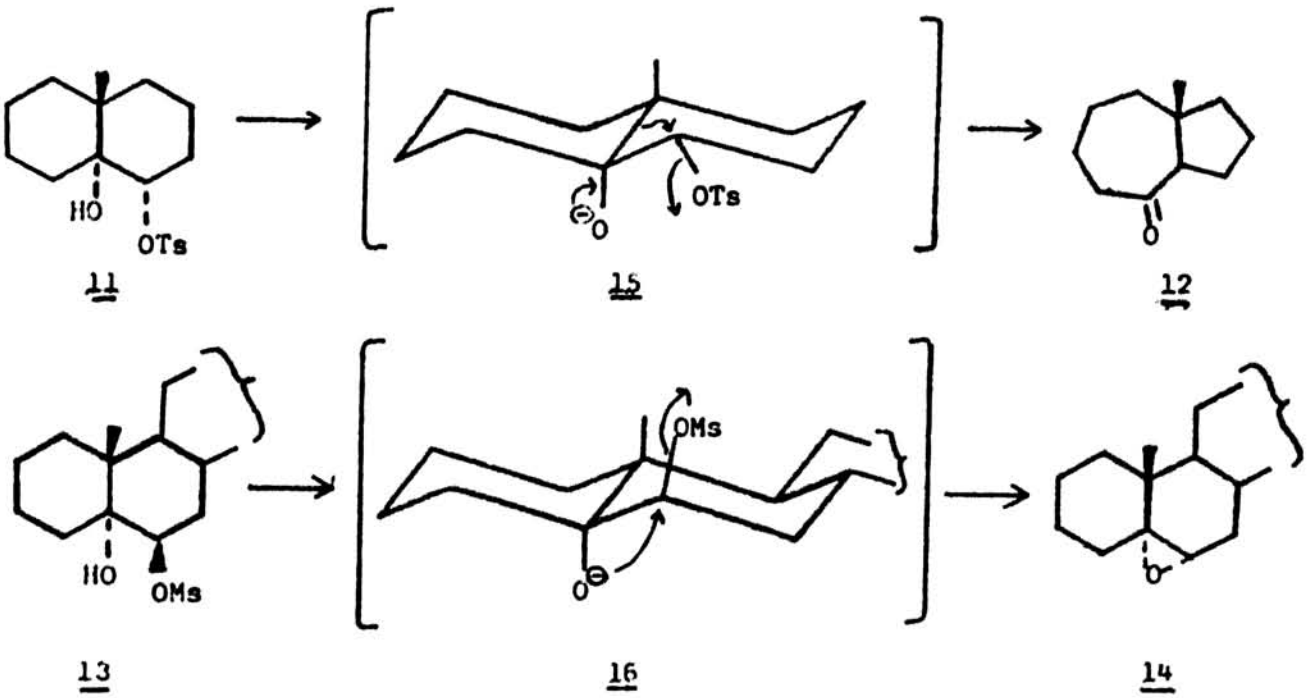


9 10

displacement of the tosylate by the initially formed anion (9) to form an epoxide.[17] The optimum conditions for formation of the epoxide by path a, as with other intramolecular displacement reactions, are a trans-coplanar relationship between the hydroxyl and tosylate functions so that the anion can attack the carbon bearing the tosylate from the backside.[18]

Reaction by path b is a base-catalyzed semi-pinacol rearrangement whereby a substituent at the carbon bearing the hydroxyl group migrates in a 1,2-fashion and displaces the tosylate from the backside to form an aldehyde or ketone. Again, the optimum conditions for 1,2-migration by path b exists when the four centers involved in the rearrangement are coplanar and the migrating and departing groups are trans and antiparallel. These requirements are well illustrated by studies of such rearrangements

in conformationally biased systems. For example, treatment of 10-methyldecalin-1,9-diol-1-tosylate (11) with potassium tert-butoxide gave 7-methylbicyclo[5.3.0]decan-2-one (12),[19] whereas treatment of mesylate 13 with the same base afforded epoxide 14.[15c] In the conformational

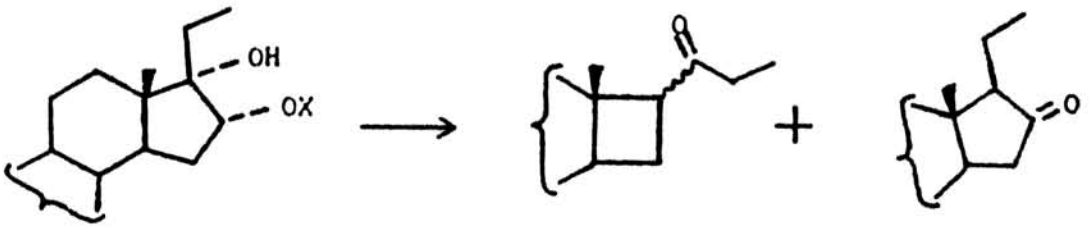


11 15 12

13 16 14

representation of intermediate anion 15, it is easily seen that the migrating C-9--C-10 bond and the departing tosylate group are trans and coplanar, hence, semi-pinacol rearrangement occurs, whereas in intermediate 16 the anion and mesylate are trans and coplanar, therefore, the lowest energy pathway is epoxide formation.

The final path c, which has been observed only with cis-1,2-glycol monosulfonates,[16a,20] involves nucleophilic attack by the initially formed anion 9 at the sulfur of the sulfonate ester with resultant S-O bond cleavage. The anion, 10, which results from such a transtosylation may then rearrange by path b. The transtosylation mode of reaction is supported by indirect evidence.[16a] For example, when mesylate 17a is treated with potassium tert-butoxide it undergoes rearrangement to give



17 (a) X = Ms
(b) X = Ts

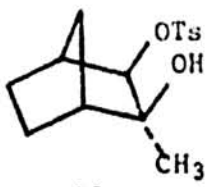
18

19

ketones 18 (72%) and 19 (28%). The corresponding tosylate sulfur atom would be expected to be less susceptable to nucleophilic attack due to resonance interaction with the aromatic system, transtosylation would be less likely to occur, hence, ketone 19 would not be formed. This was found to be the case, for when 17b was treated with potassium tert-butoxide, ketones 18 were formed almost exclusively.

E. Ghera[16a] has shown that semi-pinacol rearrangements, as well as other four centered ionic rearrangements in conformationally biased cyclohexane rings, generally follow the course imposed by the geometry of the molecule even when the electronic factors could have exercised an unfavorable influence upon the course of reaction. He[16a] also indicates a marked difference in the course of rearrangement of five-membered ring systems as a function of substituents. It does not appear that steric factors are significant enough to account for this difference. A possible reason for the different course of rearrangement in five-membered rings, as compared to six-membered rings, is that although the migrating and departing groups can be trans, coplanarity cannot be absolutely achieved, thus an alternate transformation cannot be excluded a priori.

With these principles in mind, a study of the semi-pinacol reaction of tosylate 20 was undertaken. It was our intention to observe how strictly the requirement of a trans and coplanar relationship must be adhered to in this type of transformation with this conformationally biased tosylate.



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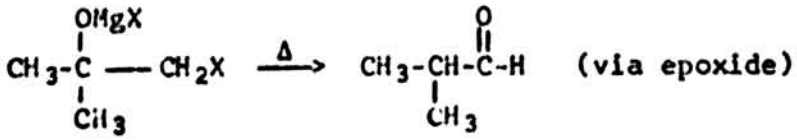
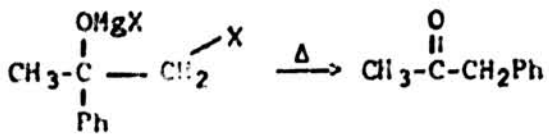
Keeping in mind what has been said about the semi-pinacolic reaction of the above monosulfonate esters, one can easily see the analogy between the reaction of the aforementioned esters and the reaction of bromohydrins. The reaction of bromohydrins under conditions to effect rearrangement has long been known and has been extensively studied.[21] The base-induced rearrangement of halohydrins can be initiated with such bases as hydroxide ,[22] Grignard reagent,[14] alkoxides,[22] hydride,[23] or the reaction can be initiated by treatment with neutral silver nitrate[22] or silver oxide.[22]

No general mechanism has been advanced, but certain conclusions have been drawn with regard to the course of the reaction in certain systems. For example, Geissman and Akawie[24] extensively studied the reaction producing ketones <u>via</u> the decomposition of the magnesium salts of halohydrins and observed that halohydrins possessing a primary halide do not rearrange unless a good migrating group is involved and that halohydrins with a secondary or tertiary halide do rearrange regardless of the migrating group (eq. 1). From their stereochemical studies they[24]

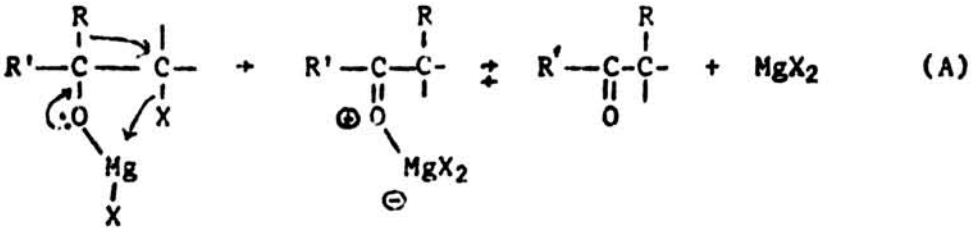


(1)

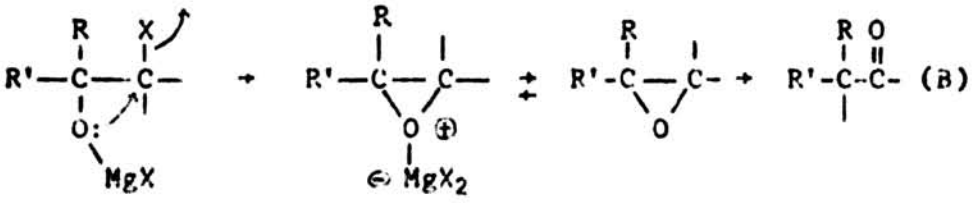


concluded that the halo and hydroxy groups must be <u>cis</u> (or able to attain

the cis alignment in non-rigid systems) to effect rearrangement. The trans isomer leads to extensive decomposition, thus, precluding an epoxide intermediate in the reaction and suggesting a semi-pinacol mechanism.[24] From these studies two mechanisms were postulated. Mechanism A should be favored when the halogen is secondary or tertiary and when the relative disposition of the halogen and -OMgX is cis, whereas mechanism B



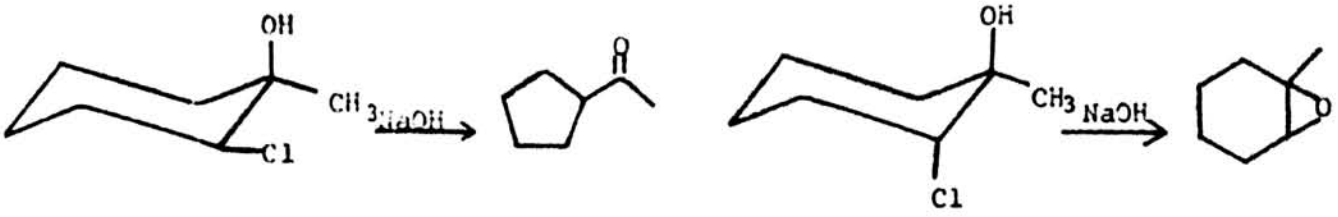
(A)



(B)

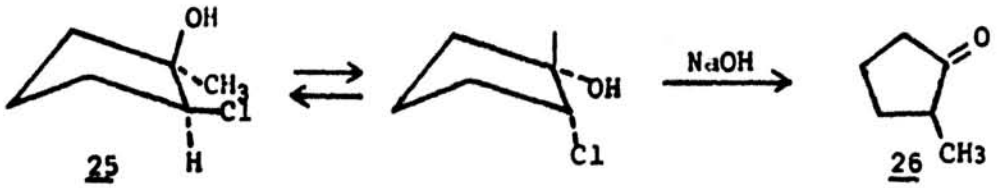
should be favored when the halogen is primary and the migrating R group has a low migratory aptitude. In later work Sisti[25] confirmed these mechanisms by effecting rearrangements in nonpolar solvents, thus leading one to believe that an intimate ion pair or a concerted mechanism must surely be followed.

However, Curtin and Harder[22] undertook a study of the reaction of cyclohexane halohydrins and found that no clear cut pathway was followed. The only conclusion that could be drawn, based on the assumption that the cyclohexane ring exists only in the chair conformation during reaction, was that the reaction path was influenced by steric control. For example, chlorohydrin 21 underwent rearrangement to give the ring contracted product 22, whereas the trans isomer, 23 gave epoxide 24. The cis five-

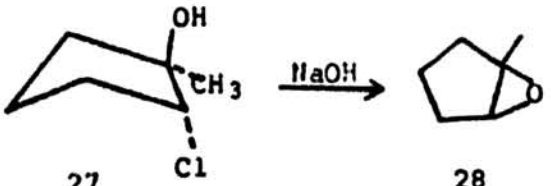


21 22 23 24

membered analog (25) gave a different type of rearrangement product, but the trans isomer (27) gave the expected epoxide.[22] In many cases



25 26

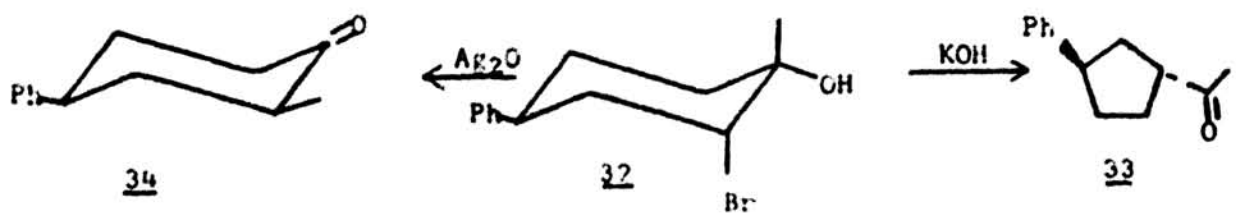


27 28

the product obtained was dependent upon whether potassium hydroxide or silver oxide was used and the corresponding epoxide was very seldom obtained with silver oxide. For example, epoxide 30 was obtained when bromohydrin 29 was treated with potassium hydroxide, but ring contracted

31 29 30

aldehyde 31 was obtained when silver oxide was used.[22] This behavior is illustrated further by the following example. In this instance ring contracted ketone 33 was obtained when bromohydrin 32 was treated with



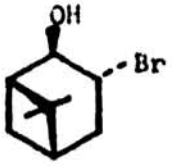
34 32 33

potassium hydroxide and ketone 34 was obtained with silver oxide.[22]

From these observations it could be concluded that the reactions do not proceed through the same intermediate and that neighboring group participation exerts a profound influence. It would also appear that the reaction involves a concerted displacement of bromide by the appropriately oriented neighboring group. Hence, potassium hydroxide would favor alkoxide formation which, if properly aligned, could give epoxide or rearranged product depending upon which neighboring group possesses the optimum geometry for displacement of the bromide. However, silver oxide in hexane facilitates bromide ion departure, hence, the group that can displace the bromide ion by backside displacement will dictate what product is formed with epoxide formation occuring only when the hydroxyl and bromine groups are trans and diaxial.

Another way to view the reaction of halohydrins is that with base a "push" mechanism is involved where electrons are pushed towards the carbon bearing the halogen, whereas with silver a "pull" mechanism would operate in which electrons would be pulled towards the electron deficient carbon.

With these concepts in mind a study of bromohydrin 35 was initiated to observe if the pinane system which contains two six-membered rings would behave similarly.



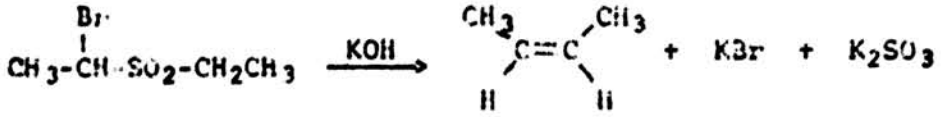
35

Ramberg-Bäcklund Rearrangement

Historical. Compounds that contain tetravent sulfur generally display reactivities which suggest that the influence of the sulfone

group parallels in magnitude and direction the effects normally produced by the usual electron-withdrawing groups such as carbonyl, cyano, and nitro.[26] A most notable exception to this behavioral pattern is the observation that the strong activating effect of carbonyl and cyano groups on the rate of displacement of an α-halogen atom is dramatically reversed by the sulfone group. From studies conducted by Bordwell and coworkers[27] this rate retardation was attributed either to a large steric effect based on the similarity of the $-SO_2CH_2-$ system to the neopentyl group, to a field effect owing to the repulsion of the nucleophilic species by the negative field of the sulfone oxygen atoms, or to a combination of the two influences.

However, in 1940 Ramberg and Bäcklund[28] reported that α-bromoethyl ethyl sulfone (36) and several related α-halo sulfones readily released halide ion when treated with excess base and were converted



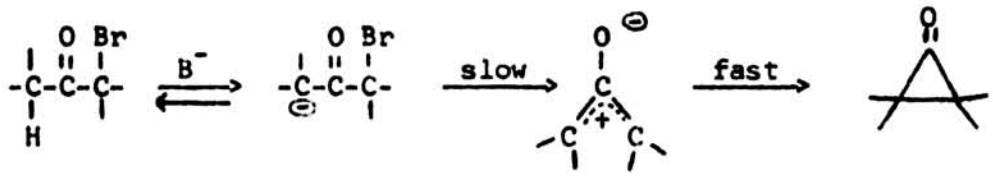
36

in good yield to alkenes in which the carbon-carbon double bond supplants the sulfone group. The remarkable feature of this reaction was that the thermodynamically less stable cis isomer was the predominant product. Since this report was published this reaction has been the subject of numerous investigations[29] and has become known as the Ramberg-Bäcklund reaction.

Mechanism. Before mechanistic studies were done on the Ramberg-Bäcklund reaction, a mechanism similar to that of the related Favorskii rearrangement[30] was thought to be operative. This mechanism involves

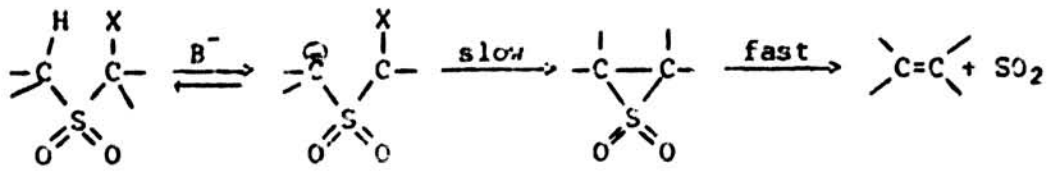
an initial rapid and reversible enolate anion formation with subsequent ejection of halide ion to form a delocalized zwitterion which can then collapse in a disrotatory fashion to the cyclopropanone intermediate (Scheme I). The rate determining loss of halide ion does not involve an intramolecular Sn2 displacement. Instead, it is the result of carbon-halogen bond ionization which is assisted by interaction of the π-orbitals of the proximate enolate anion function.

Scheme I



From kinetic investigations[31] of the Ramberg-Bäcklund rearrangement of several α-chlorosulfones with hydroxide ion, the rate of release of halide ion from an α-halo sulfone was shown to be first order in both hydroxide ion and sulfone. These data suggest an initial rapid preequilibrium between the sulfone and its anion, followed by an intramolecular 1,3-displacement of chloride ion and rapid expulsion of sulfur dioxide from the episulfone intermediate (Scheme II).

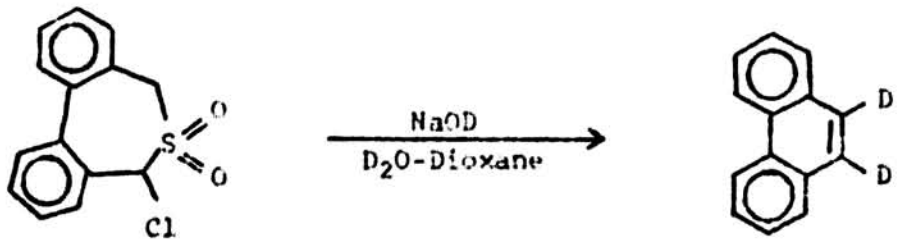
Scheme II



Each aspect of this proposed mechanism will be dealt with separately and evidence will be given to support the postulated pathway. The prin-

cipal questions for which answers will be supplied are the following. (a) Is the carbanion formed in a preequilibrium step? (b) What is the mechanism of halide loss? (c) What is the mechanism of sulfur dioxide extrusion?

a. Proton Abstraction. There is ample evidence that a preequilibrium does take place. For example, reaction of α-chloro sulfone 37 with sodium deuteroxide in deuterium oxide was found to give olefins which were completely deuterated at the vinyl positions.[32] The same results were also obtained when α-chloroethyl ethyl sulfone (38) was treated under identical conditions.[32] The possibility that exchange was taking place at a later stage of the reaction was eliminated when α-bromo sulfone 39 was treated with sodium methoxide in methanol-d and



37

$CH_3CH_2-SO_2-CHClCH_3$ $\xrightarrow[D_2O\text{-Dioxane}]{NaOD}$ $CH_3CD=CDCH_3$

38

reaction was allowed to proceed for one half-life. The recovered α-bromo sulfone, 40, showed complete deuterium incorporation at the α and α' positions.[33]

$C_6H_5CH_2-SO_2-CHBrC_6H_5$ $\qquad$ $C_6H_5CD_2-SO_2-CDBrC_6H_5$

39 $\qquad$ 40

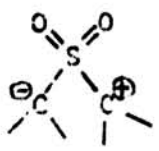
b. Halide Loss and Cyclization. Establishment of the intervention of carbanions in a preequilibrium does not conclusively establish that a

carbanion is necessarily on the reaction pathway leading to the observed olefins.[34] It could be that their formation is merely coincidental to the concerted mechanistic path. Disproven alternative mechanisms for halide ion loss and the cyclization step involve the formation of carbene or zwitterion intermediates and a concerted displacement. A carbene pathway is unlikely to be operating because (a) α,α-dichloro and α,α,α-trichloro sulfones, systems which are incapable of forming carbenes, readily undergo base-induced rearrangements; (b) phenyl substitution on the α-carbon causes rate acceleration,[31] whereas its inductive affect should retard the rate of α-elimination; and (c) certain α-chloro sulfones such as 41 and 42, which are capable of undergoing α-elimination, but not 1,3-elimination give no products derivable from carbenoid intermediates

$C_6H_5\text{-}SO_2\text{-}CH_2Cl$ (41) $\qquad$ $(CH_3)_3C\text{-}SO_2\text{-}CH_2\text{-}Cl$ (42)

and, in fact, lose chloride ion only very slowly when treated under Ramberg-Bäcklund reaction conditions.[33] Collectively, these observations strongly imply that a carbanion does indeed occupy a position on the reaction pathway leading to the olefinic products.

The intervention of dipolar ions similar to those proposed in the related Favorskii reaction have been ruled out because the formation of zwitterion 43 would be quite energetically unfavorable principally due



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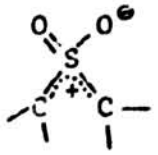


43a

to the strong electrostatic repulsion associated with the close proximity of positive centers. This electrostatic repulsion would be expected to be sufficient to raise the free energy of activation too high for heterolysis to occur readily. Also to be noted, a symmetrical structure such as 43a would be expected to give the same cis:trans olefin ratio for isomeric α-halo sulfones, which has been shown not to occur.[36]

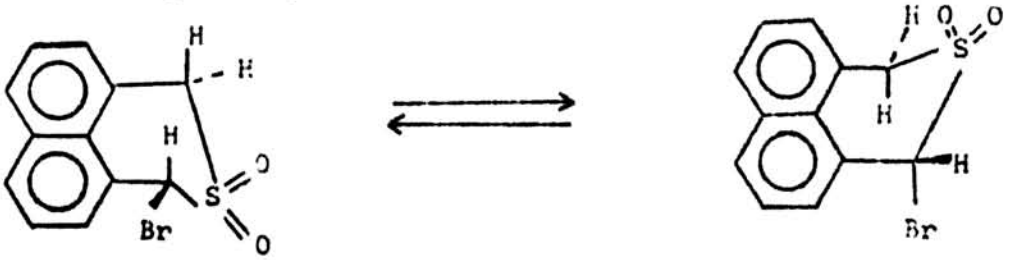
Experimentally it is difficult to distinguish between a step wise and concerted mechanism, however, from results that have been reported to-date, it appears quite likely that base induced 1,3-eliminations, in general, occur by two-stage mechanisms, and that the one-step, concerted mechanism, is rare or nonexistent.[36] Convincing evidence has been presented that strongly suggests that a concerted mechanism is not operative in this reaction. For example, it has been shown that α-halo sulfones 39 and 44 exhibit an unusually large leaving group effect when treated

$C_6H_5CHBr\text{-}SO_2\text{-}CH_2C_6H_5$ (39) $\qquad$ $C_6H_5CHCl\text{-}SO_2\text{-}CH_2C_6H_5$ (44)

under rearrangement conditions (Br:Cl rate ratio = 620 at 0°).[33] These results are more conveniently rationalized in terms of a carbanion mechanism.

Since a concerted mechanism would require a coplanar alignment of the H-C-S-C-Br atoms in the transition state, a bromo sulfone, for example, 45, in which this alignment of atoms is made facile (or mandatory) for stereochemical reasons would be expected to undergo a more rapid rearrangement than its open-chain analog, 39. However, it was shown[37] that 39 reacts ca. 7.5 times faster and the activation parameters for the two

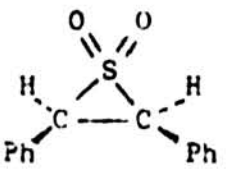
were nearly identical. These results strongly suggest that a concerted mechanism is surely not operative.



45

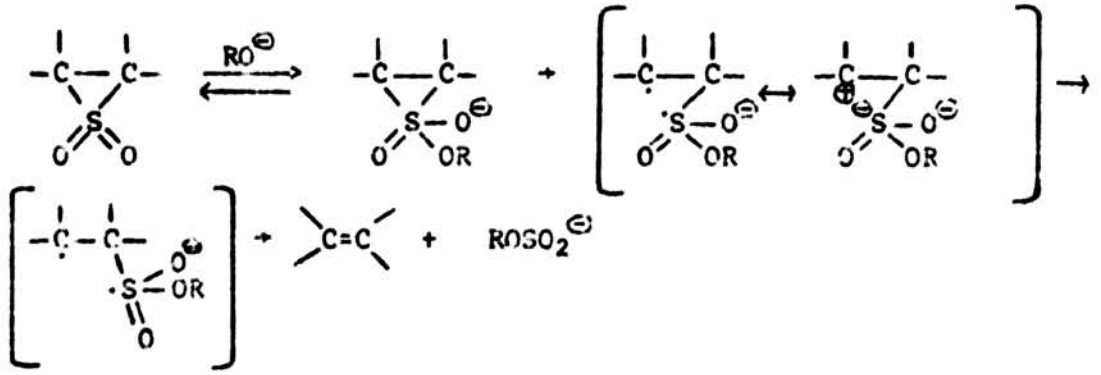
Episulfone intermediates have not been isolated from any Ramberg-Bäcklund reaction because the alkaline conditions needed for rearrangement are sufficiently strenuous that decomposition of these intermediates occur concomitantly. Even though episulfone intermediates cannot be prepared by the Ramberg-Bäcklund reaction overwhelming evidence has been presented supporting their existence as a reaction intermediate. The best piece of evidence for the presence of such proposed intermediates comes from a study by Neureiter[38] in which he studied the decomposition of different sulfones under the conditions of the Ramberg-Bäcklund reaction and found that the episulfones decomposed in a stereospecific manner and gave the same cis:trans olefin isomer ratio as was obtained from the corresponding α-halo sulfones in the Ramberg-Bäcklund reaction. These results indicate that the portion of cis- and trans-alkenes formed in the reaction are a reflection of the portions of cis- and trans-episulfones that are formed in the reaction.[38]

A notable exception to this generalization was observed in that a strong base such as tert-butoxide was found to epimerize the episulfone before decomposition could occur, thus changing the cis:trans product ratio. Also, episulfones with acidic hydrogens such as 46 were found to be epimerized with weaker bases and showed similar changes in product ratios.[39]



46

c. Extrusion of Sulfur Dioxide. The mechanism of the final step, extrusion of sulfur dioxide to give the olefinic products, has been evasive in that a definite mechanism for this extrusion has not been established, but evidence has been presented that indicated certain pathways could be operative. It was found that base has a tremendous accelerating effect on the decomposition of episulfones and the following mechanism has been postulated. However, in the absence of base, the



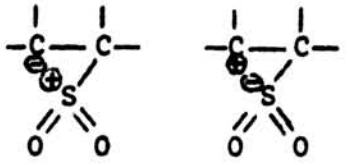
pathway is not so clear. Three possible mechanisms for the thermal decomposition of the episulfone intermediate could be operative: (a) concerted; (b) dipolar; or (c) diradical.

The stereospecific decomposition of episulfones is surprising in that Woodward-Hoffmann[34] symmetry selection rules predict that concerted decomposition is symmetry forbidden. This plus the fact that the rate of decomposition is dependent upon the ionizing power of the solvent[46] strongly suggest that a nonconcerted mechanism is being followed.

Two final points favoring a nonconcerted mechanism are the above study which showed that decomposition is accelerated by base[38] and the

observation that photodecomposition of several episulfones occurs to the extent of 80-90% at -78° (in agreement with Woodward-Hoffmann predictions[39]), whereas in the absence of irradiation less than 20% decomposition occurs.

Dipolar intermediates such as 47 are quite unlikely because one would expect the formation of solvent derived products when alcoholic solvents are employed, but none have been observed.[40]



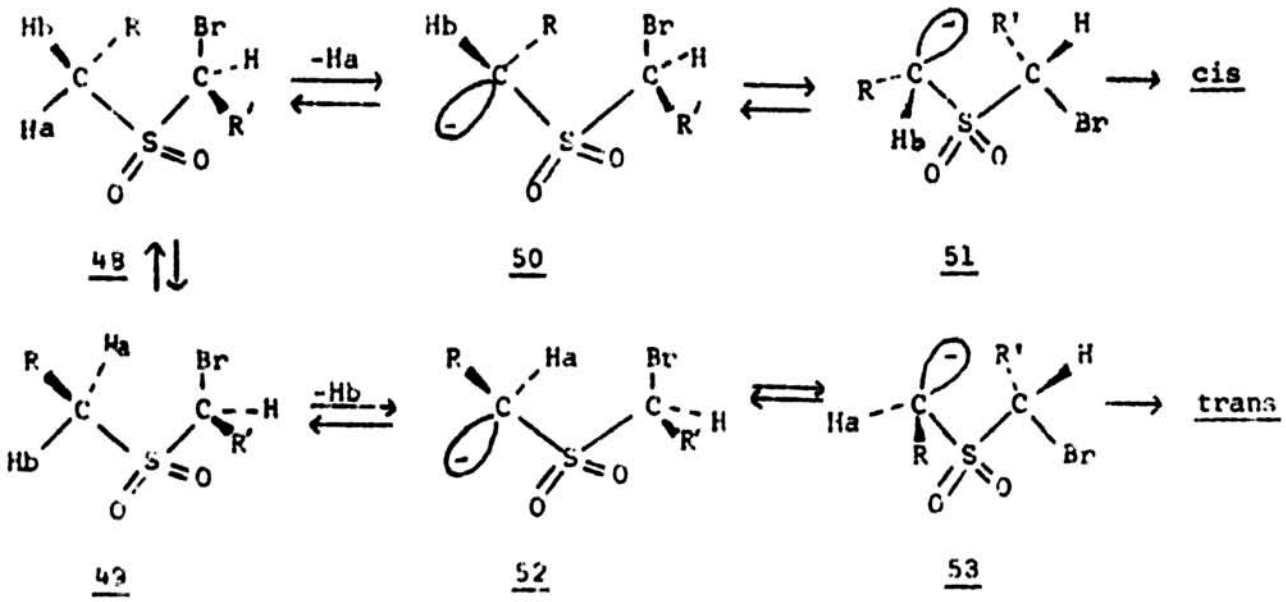
47

Evidence has been presented which suggests that such sulfur dioxide expulsions from episulfones proceed via 1,3-diradical intermediates, which possess significant rotational barriers.[39] The observation that stored samples of episulfones always give some polysulfones support this diradical mechanism. The acceleration of episulfone decomposition in the presence of base can be interpreted in terms of a diradical anion intermediate arising from initial addition of base to the sulfone group, although the exact moment of sulfur-oxygen bond formation remains unknown.

Stereochemistry. The steps in the mechanism have been substantiated, but fail to account for the remarkable stereospecificity of the reaction noted in acyclic sulfones. The most satisfying explanation is illustrated by Scheme III.[41] It has been found that α-sulfone carbanions are protonated from the direction syn to the sulfone oxygens.[42] On the basis of microscopic reversibility it must be concluded that α-sulfone protons are preferentially abstracted by base when they are flanked by the two

oxygens of the sulfone grouping. The deprotonation of 48 (the more stable conformer) to give carbanion 50 (effectively planar with a rotational barrier) and concomitant rehybridization of the α'-sulfone carbon atom to give 51 would appear to be the lower energy pathway because of

Scheme III



less steric compression in 50 than in 52 and eclipsing of smaller groups in going from 50 to 51 than in going from 52 to 53.

The Curtin-Hammett principle which is based on transition-state theory points out that product composition in no way reflects the relative energies of the ground state conformers but only the relative energies of the respective transition states.[43] The lower energy of the cis-episulfone transition state in reality reflects the lowest energy pathway available to 48 for the reasons just presented.

Summary. The following points should be noted. The cis:trans ratio of olefin products is not greatly affected by changes in the nature of the halide, the nature of the base, with the exception of tert-butoxide,

or the size of the alkyl group flanking the sulfone,[38] but the per cent of cis-alkene decreases with increasing size of alkyl groups.[41] The stereochemistry of the product is determined in the episulfone formation step. The relative rate of halide ion release is I > Br > Cl[33] and the yield of olefins is greater when the halide ion is on the less bulky substituent. Whether or not sulfur dioxide expulsion acceleration will occur depends on the reaction conditions employed. Low temperatures, high base concentration, and a relatively nonpolar solvent will favor acceleration by base, whereas, high temperatures, low base concentrations, and an aqueous solvent will bring about decomposition by a thermal process.[29a]

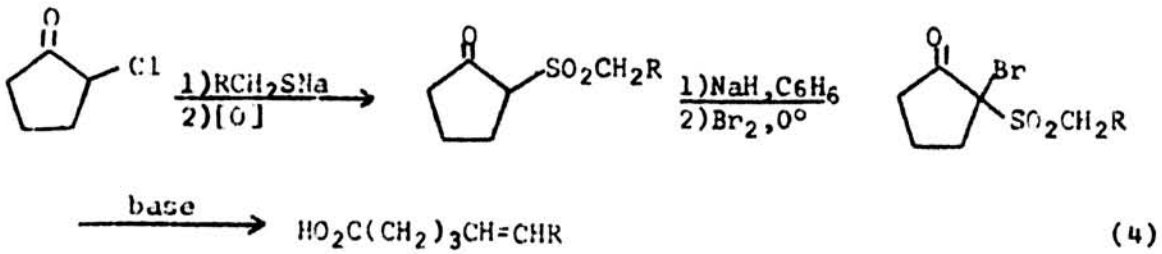
Synthetic Applications. Although there are numerous other routes to alkenes, the Rämberg-Backlund reaction should not be overlooked because of its generality and minimal production of side products. Synthetic applications include the homologation of olefins (eq. 2),[44] preparation of olefins deuterated at the vinyl position (eq. 3),[32] conversion of cyclic α-halo ketones into acyclic carboxylic acids containing a double bond at a well defined position in the carbon chain (eq. 4)[45] and the preparation of unsaturated propellanes (eq. 5).[46] These reactions are depicted in Scheme IV.

Scheme IV

$$RCH{=}CH_2 \xrightarrow[2)\ \text{hydrol.}]{1)\ AcSH,h\nu} RCH_2CH_2SH \xrightarrow[2)\ [O]]{1)\ CH_2O,HCl} RCH_2CH_2SO_2CH_2Cl$$

$$\xrightarrow{\text{base}} RCH_2CH{=}CH_2 \qquad (2)$$

$$CH_3CH_2SO_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3 \xrightarrow[D_2O]{NaOD} CH_3CD{=}CDCH_3 \qquad (3)$$



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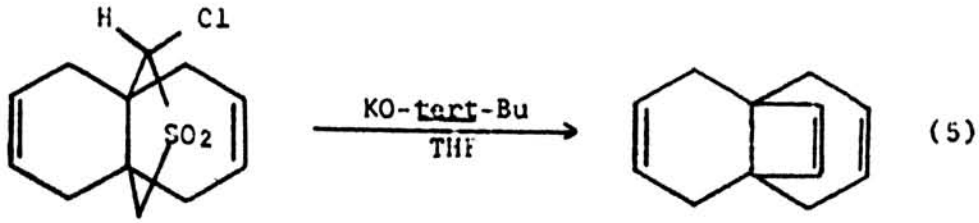
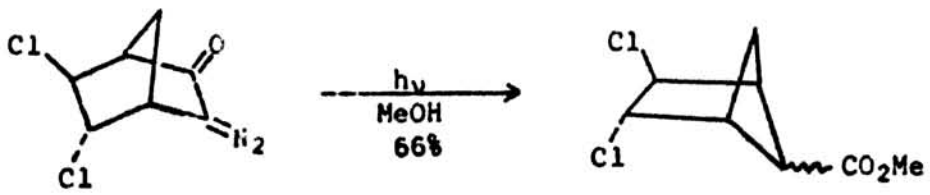


(5)

Possible Synthetic Entries into the Bicyclo[2.1.1]hexane System

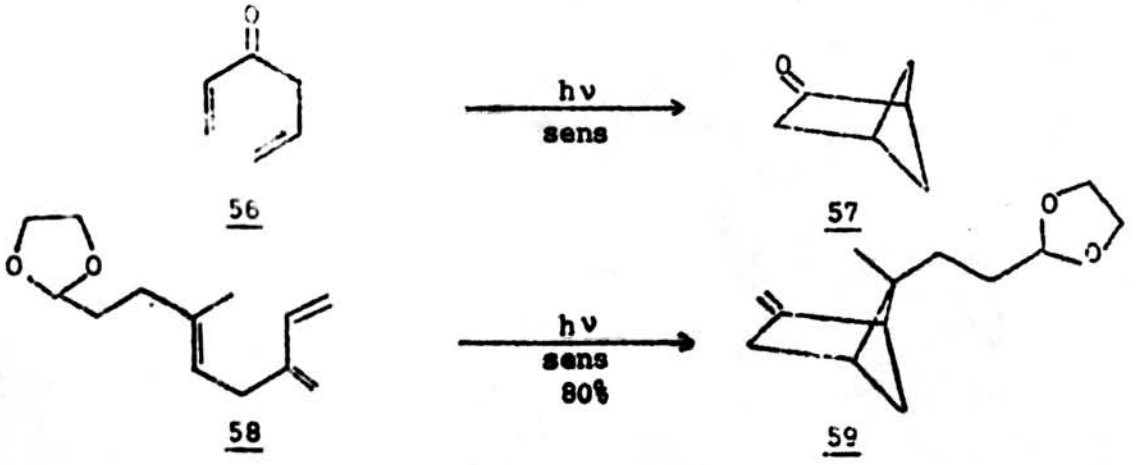
Interest in the chemistry of the bicyclo[2.1.1]hexane system has remained at a high level and as a result of this many investigations have been performed to find suitable synthetic pathways for obtaining this class of compounds from commercially available starting materials and by procedures which can be operated on a reasonable scale.[47] Although several different syntheses of bicyclo[2.1.1]hexanes have appeared, the method of demonstrated general utility is the photochemical decomposition of α-diazoketones.[48] For example, photolysis of a methanol solution of diazoketone 54 affords the isomeric esters 55 in good yield.[48a]



54 55

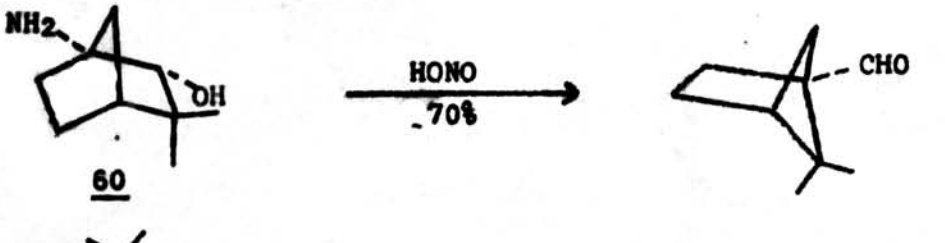
Another photochemical synthesis of the bicyclo[2.1.1]hexane system involves the photosensitized intramolecular cycloaddition of 1,5-hexadienes.[49] For example, sensitized irradiation of ketone 56 gives a 41% yield of the cyclized ketone 57.[49a] This reaction is exemplified

further by the conversion of olefin 58 to cyclized product 59 in good yield.[49c]



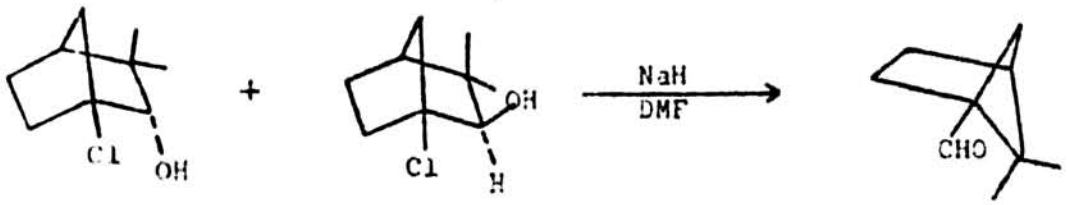
56 57 58 59

Until recently, the only purely chemical routes to the bicyclo-[2.1.1]hexane system have involved either long synthetic routes or transformations that proceed in very poor yields. The most successful chemical route developed so far appears to be the pinacolic rearrangement of suitably substituted bicyclo[2.2.1]heptane[23, 50] and bicyclo[3.1.1]heptane systems.[51] The deamination of aminoalcohols 60 and 61 with nitrous acid affords the corresponding aldehydes in good yield.[50] A similar transformation was found to occur when the corresponding halohydrins



60 61

62 was treated briefly with sodium hydride in dimethyl formamide.[23] Carlson and Pierce[51] have shown that the bicyclo[2.1.1]hexane system can easily be obtained by the pinacolic rearrangement of tosylate 63.



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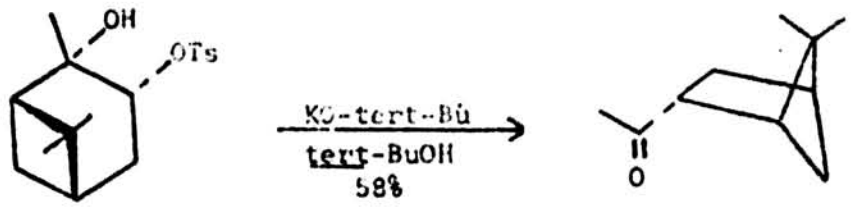
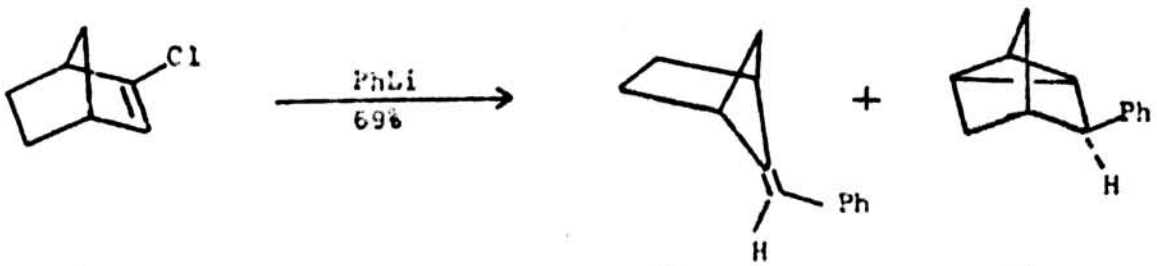
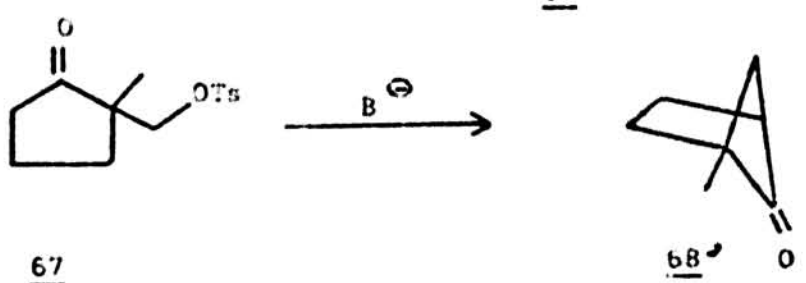


63

Other synthetic routes leading to the bicyclo[2.1.1]hexane system have been developed, but their synthetic utility is questionable because of their usually low yields. The reaction of chloro olefin 64 with phenyl lithium was found to undergo a unique rearrangement to give a 9:1 mixture of ring contracted product 65 and insertion product 66,[52] respectively. Intramolecular cyclization of tosylate 67 with potassium tert-butoxide led to ketone 68 in meager yield.



64 65 66

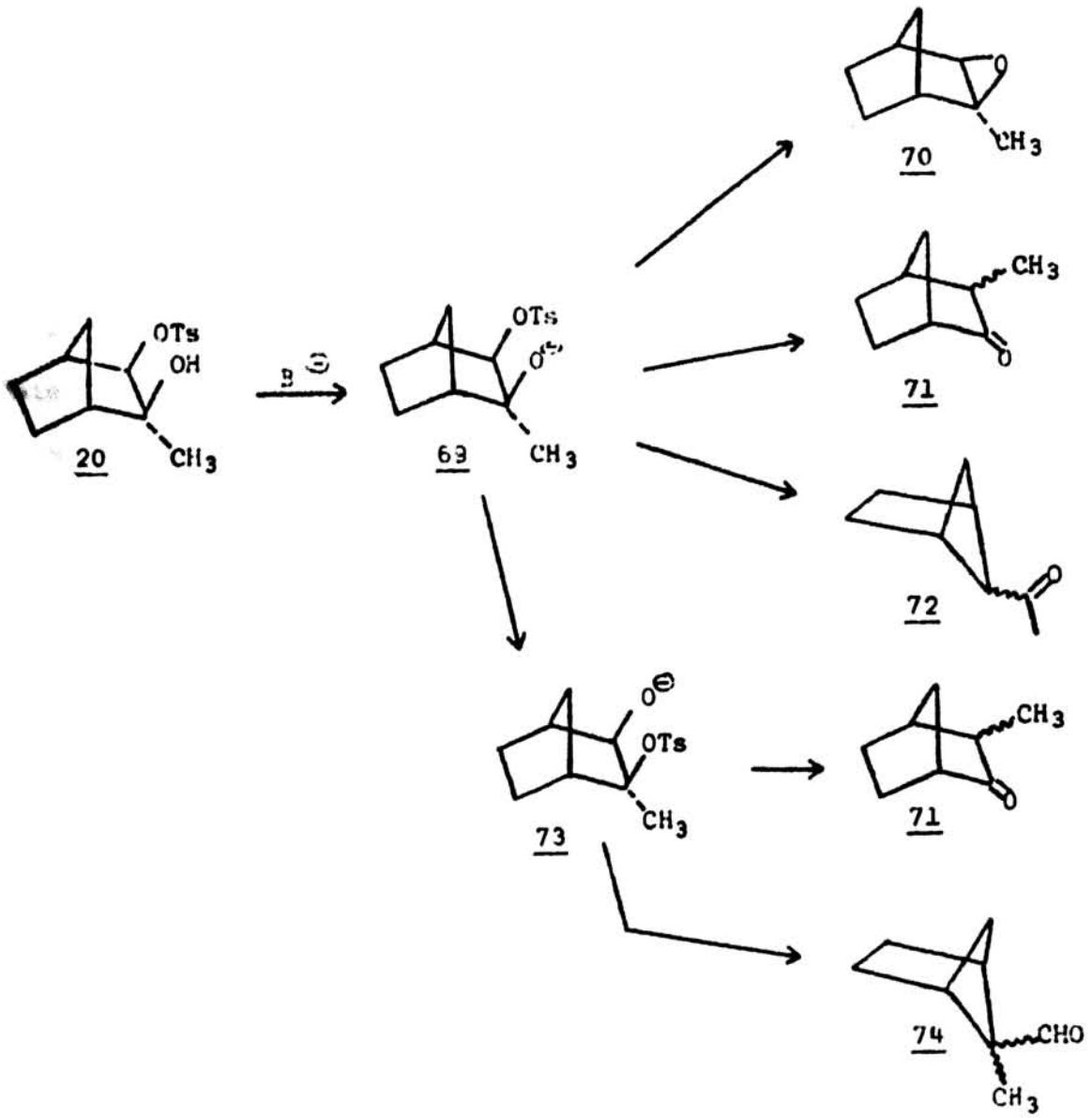


67 68

During the present investigation of the semi-pinacol rearrangement of tosylate 20, it was speculated that if this tosylate reacted in a manner similar to that of 63 the synthetic entries into the bicyclo-[2.1.1]hexane system would be broadened because of the short route from readily available starting materials (see Discussion section).

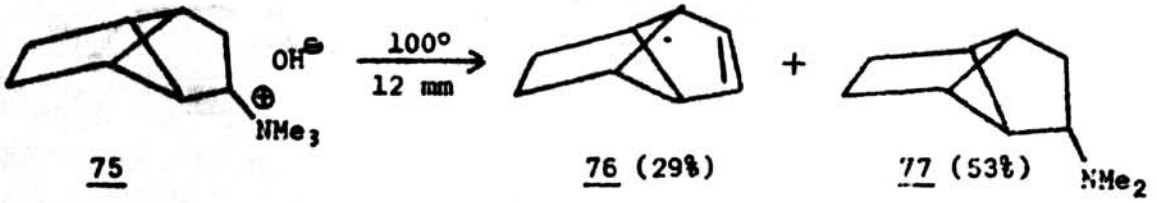
The reaction paths available to tosylate 20 upon treatment with base are depicted in Scheme V along with the possible product obtained from each pathway. Anion 69 could collapse to epoxide 70, which would

Scheme V



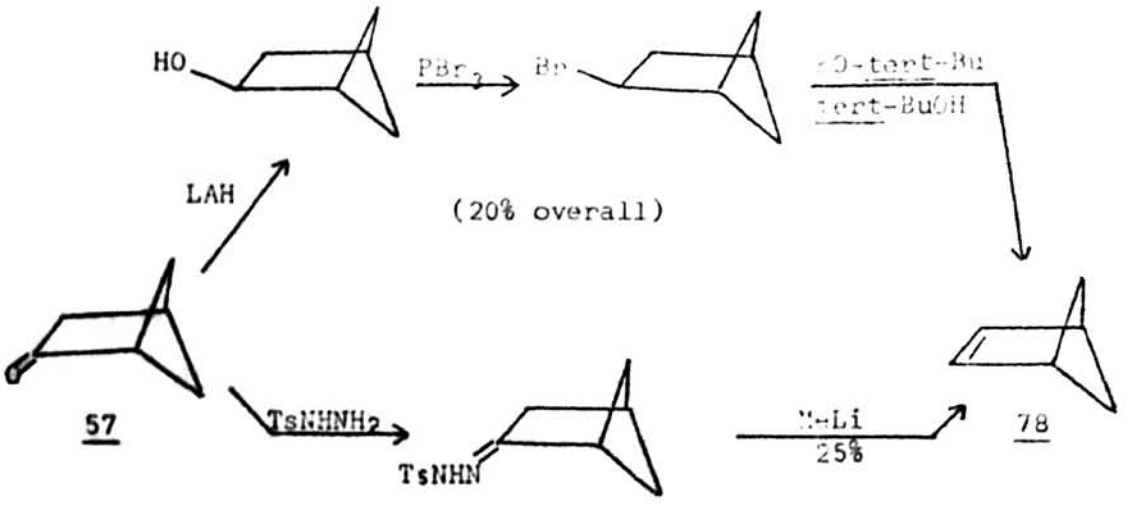
arise from the elimination of the tosylate group by the alkoxide. Ketones 71 and 72 would arise from either methyl migration or migration of the C-1--C-2 bond, respectively. Each migration has equal opportunity to occur because the C-1--C-2 bond and the methyl group occupy identical spatial positions with respect to the leaving tosylate group. If anion 69 undergoes transtosylation to give 73 and then rearrangement, again two products are possible. Ketone 71 would arise from hydride migration, whereas, aldehyde 74 would arise from C-3--C-4 bond migration. Here also, each type of migration has equal likelihood of occuring for the previously stated reasons.

It was hoped that the bicyclo[2.1.1]hexane system could also be reached utilizing the Ramberg-Bäcklund reaction. If success was to be realized, the highly strained bicyclo[2.1.1]hexene system would be obtained which has the additional feature of containing a carbon-carbon double bond. Because of the highly strained nature of this system, no efficient synthetic route has been found. The routes investigated to-date have been lengthy and proceed in very low overall yield. For example, the amine salt 75,[54] was converted in low yield to a mixture

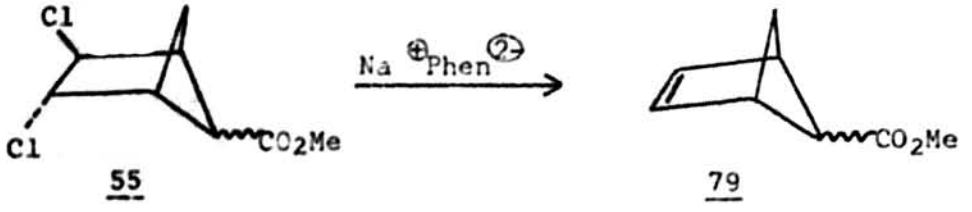


75 76 (29%) 77 (53%)

of olefin 76 and amine 77. Soon after this conversion was reported, two procedures were published in which ketone 57 was converted into bicyclo[2.1.1]hexene (78) in low yields.[55]



A more recent synthesis has been published in which esters 55[48a] were converted to olefin 79 in ca 90% yield. Even though the last step is efficient, it must be kept in mind that the required starting material is obtained only by a lengthy route. Other routes that have been attempted, but were all unrewarding, include Hoffmann elimination, amine oxide pyrolysis, acetate pyrolysis and xanthate ester pyrolysis of appropriately substituted bicyclo[2.1.1]hexane systems.[55]

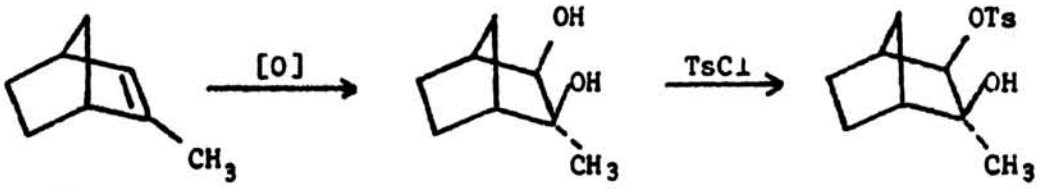


55 79

DISCUSSION

Synthesis and Rearrangement of 2-endo-Methyl-2,3-cis,exo-norbornanediol 3-p-Toluenesulfonate

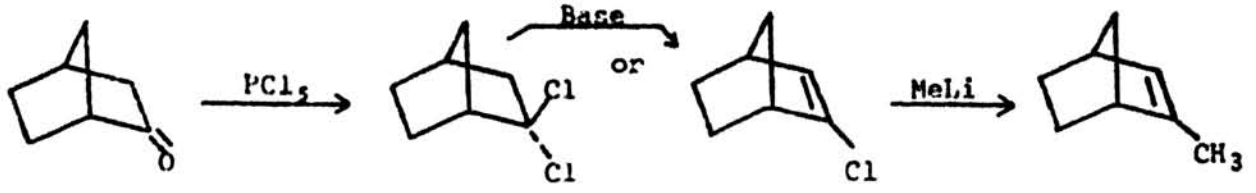
Before a study of tosylate 20 could be made, a synthesis of the precursor cis-diol 80 had to be developed. An attractive starting point appeared to be 2-methylnorbornene (81) because treatment with a suitable oxidizing agent should yield cis-diol 80 directly.



81 80 20

This scheme could not be investigated until a source of olefin 81 was found. Since this olefin was not commercially available and most of the reported syntheses[56] of this compound afford low yields, large amounts of by-products, or used precursors that were not readily available, an alternative route to this compound was sought.

Norcamphor (82) seemed to be a logical starting material because it possesses the required bicyclic ring structure and the ketone function should easily be converted to the vinyl methyl group by standard procedures. A method for the conversion of ketone 82 to olefin 81 is depicted in the following reaction sequence.



82 83 84 81

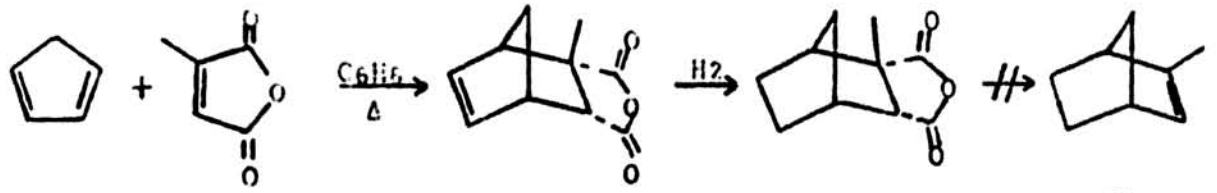
Aliphatic ketones are known to undergo halogenation[57] with phosphorus pentachloride to afford gem-dichlorides and if the ketone has an α-hydrogen, dehydrohalogenation can occur during the reaction to give the corresponding vinyl chloride as a by-product. In some cases the chloro olefin becomes the major product. Treatment[58] of norcamphor (82) with phosphorus pentachloride in refluxing methylene chloride afforded dichloride 83 as the major product along with minor amounts of olefin 84 and unidentified by-products. Based on arguments presented by Wilt and coworkers,[59] the by-products were thought to have arisen by rearrangement to give 1,2-dichloronorbornane. Even though the by-products were easily removed by vacuum distillation, a procedure was sought in which lower temperatures would be used in hopes of preventing formation of unwanted material. Following the procedure of Bixler and Niemann[60] in which norcamphor (82) was treated with phosphorus trichloride and phosphorus pentachloride at 0°, the dichloride 83 was obtained free of by-products.

Dichloride 83 was found to be quite resistant to dehydrohalogenation using a variety of bases and solvents. This was somewhat surprising because it had been reported[61] that 83 was converted to chloro olefin 84 upon treatment with potassium tert-butoxide in tert-butyl alcohol. Potassium tert-butoxide in dimethyl sulfoxide[62] gave olefin 84 in good yield.

Attempted conversion of chloro olefin 84 to 2-methylnorbornene (81) using an ether solution of methyllithium[63] failed. No reaction products were obtained after extended periods of reaction.

An alternative route to olefin 81 was then investigated. Radlick and coworkers[64] have decarboxylated a series of 1,2-diacids to the corresponding olefins by basic electrolysis. This appeared encouraging

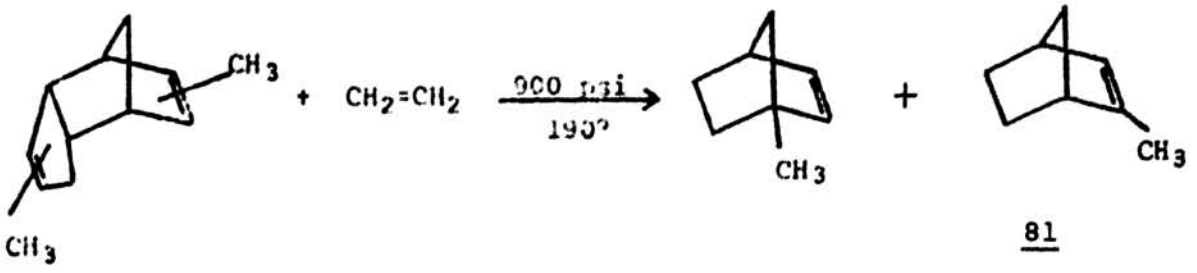
because the precursor diacid, for our case, can easily be obtained as depicted in the following reaction sequence. However, when this oxidative



81

decarboxylation was attempted no desired olefin 81 was isolated.

In a private communication from C.W. Jefford,[65] it was pointed out that olefin 81 could be obtained in good yield by utilizing the Diels-Alder reaction between commercially available methylcyclopentadiene and ethylene at elevated temperature and pressure.[66] This procedure afforded the desired olefin in good yield after distillation to remove the 1-methylnorbornene isomer. Taking advantage of the commercial availability of starting material and ease of reaction, olefin 81 could be prepared in large quantities.

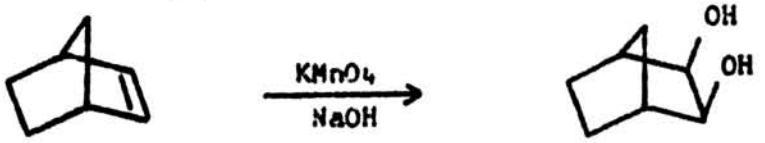


81

Now that a source of olefin 81 was at hand, the conversion of it to diol 80 could be investigated. This transformation has been reported to occur in unspecified yields when olefin 81 was treated with an equivalent amount of osmium tetroxide.[67] Because osmium tetroxide oxidation of olefins supposedly is a very efficient procedure for accomplishing cis-hydroxylation, we hoped to apply this sequence to our system so as to obtain large, workable quantities of cis-diol 80. The high cost and toxic

nature of the oxidant at first diminished our hopes of following this scheme. However, these obstacles can be circumvented by following a procedure[68] in which only a catalytic amount of osmium tetroxide is used in the presence of a much cheaper oxidant, such as sodium chlorate, that can regenerate the osmium tetroxide during the course of the reaction. A very important requirement of the supplemental oxidant is that it does not alter the course of the reaction. When olefin 81 was subjected to these reaction conditions[68] a very complex mixture of products was obtained in low yield.

Failure to obtain cis-diol 80 using osmium tetroxide directed our attention back to the common, but inefficient, oxidation of carbon-carbon double bonds with potassium permanganate.[69] Wiberg and Seagebarth[70] have shown that cis-hydroxylation with basic permanganate of norbornene (85) occurs from the least hindered side to give cis-diol 86. It was speculated that olefin 81 should follow a similar course because the

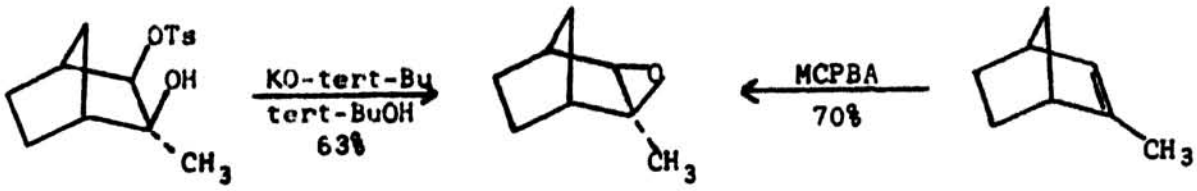


85 86

additional methyl group should not introduce any new steric requirements that might change the course of the reaction. Oxidation of olefin 81 with dilute basic permanganate[70] afforded cis-diol 90 in moderate yield. Although the yields are not high, the simple procedure could be performed on a large scale with a minimal formation of over oxidized products.

Treatment of a pyridine solution of cis-diol 80 with p-toluenesulfonyl chloride afforded tosylate 20 in good yield, which could be recrystallized and was thermally stable. Treatment of tosylate 20 with potassium tert-butoxide in tert-butanol at 65° for eight hours produced

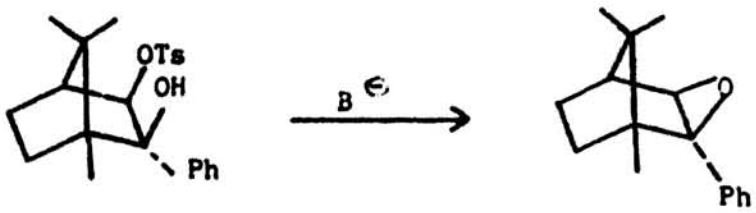
a clear liquid which was shown by vpc analysis to be ca. 100% pure in one component. The ir spectrum of the product did not show the presence of any carbonyl or hydroxyl groups, but did show carbon-oxygen stretching. Based on this data, the product was assigned structure 87.



20 87 81

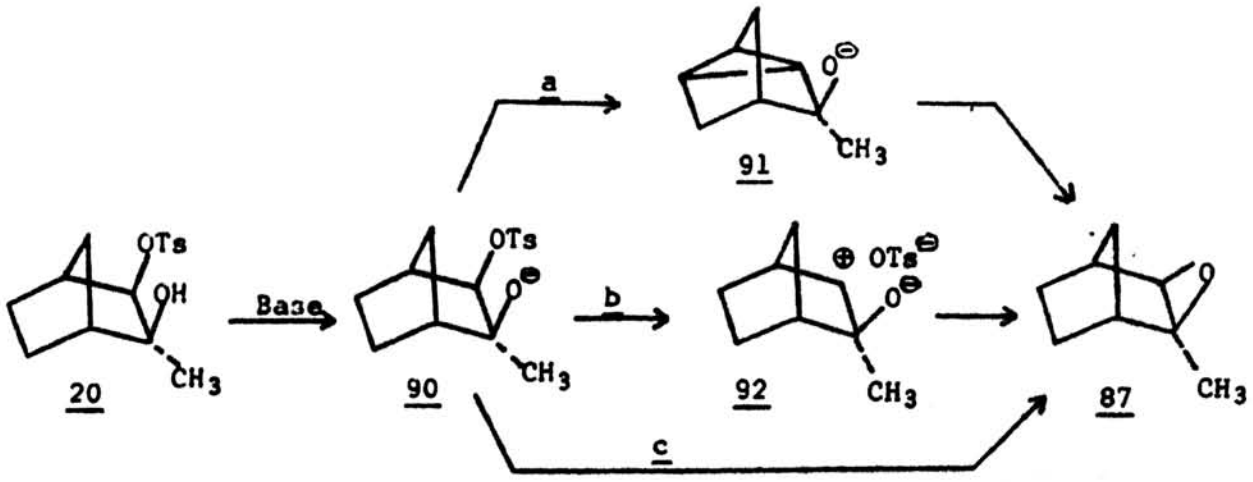
To verify epoxide formation, an independent synthesis for the epoxide was carried out. Brown and coworkers[71] have shown that epoxidation of bicyclo[2.2.1]heptenes occurs in a predictable and stereospecific manner. Applying this procedure to olefin 81, using m-chloroperbenzoic acid, only one isomeric epoxide was obtained which was assigned the stereochemistry depicted in structure 87. The ir spectrum of this epoxide and that of the product from the reaction of tosylate 20 with potassium tert-butoxide were superimposible, thus confirming epoxide formation.

Although the formation of this epoxide was unexpected, this epoxide formation is not without precedent. Coxon and coworkers[72a-c] reported that tosylate 88 upon treatment with base afforded epoxide 89 in moderate yield. Three mechanisms can be suggested which can account for the formation of epoxides 87 and 89. The first, path a, which involves a 1,3-elimination on alkoxide 90 to form the nortricyclene 91, which could then



88 89

undergo protonation at C-5 to give epoxide 87. This mechanism is unlikely because it has been observed[72d] that the nortricyclene compound is stable to the reaction conditions used here.



The second possible pathway, path b, would involve solvolysis of the tosylate group to give a tight ion pair 92, which could then close to give epoxide 87. The last pathway, path c, involves front side attack of the alkoxide anion with concurrent elimination of the tosylate leaving group. Sufficient experimental evidence has not been obtained to distinguish between the latter two mechanisms.

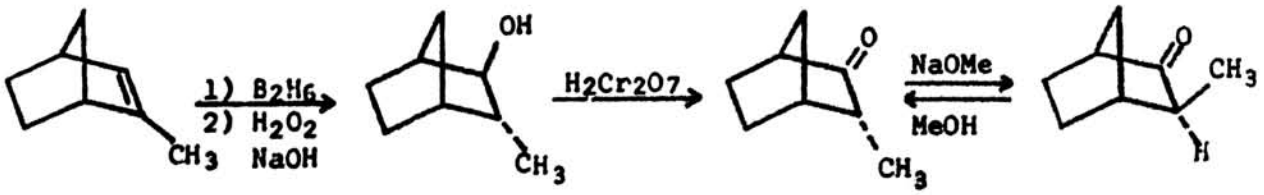
Coxon and coworkers[72a-c] speculate, and we tend to agree, that the latter mechanism, path c, is operative. One bit of evidence that may support path c and argue against, but not eliminate, the formation of a tight ion pair, path b, is that norbornyl cations are known to undergo facile rearrangement,[73] but no such products were isolated in the reaction of 20 with base.

From these observations it appears that the energy requirement for front side elimination is considerably less than for carbon migration to give rearrangement products in the bicyclo[2.2.1]heptane system under

these reaction conditions. Models show that a true trans and coplanar relationship, which is required for backside displacement,[18] cannot be achieved between the C-1--C-2 bond and the tosylate leaving group, whereas, in the front side elimination process the intermediate alkoxide anion can approach the side of the C-3--tosylate bond and aid its displacement.

In order to test the generality of the reaction regardless of the base, tosylate 20 was treated with lithium bis(trimethylsilyl)amide in tetrahydrofuran with a dilute acid workup, to destroy the base, afforded a mixture that was shown to consist of ketone 94 (76%) and 24% unidentified product. Similarily, potassium tert-butoxide in tetrahydrofuran gave a complex mixture that was shown to contain ketones 94 (31%) and 95 (17%).

Ketones 94 and 95 were identified by comparison to authentic samples prepared by the following reaction sequence.



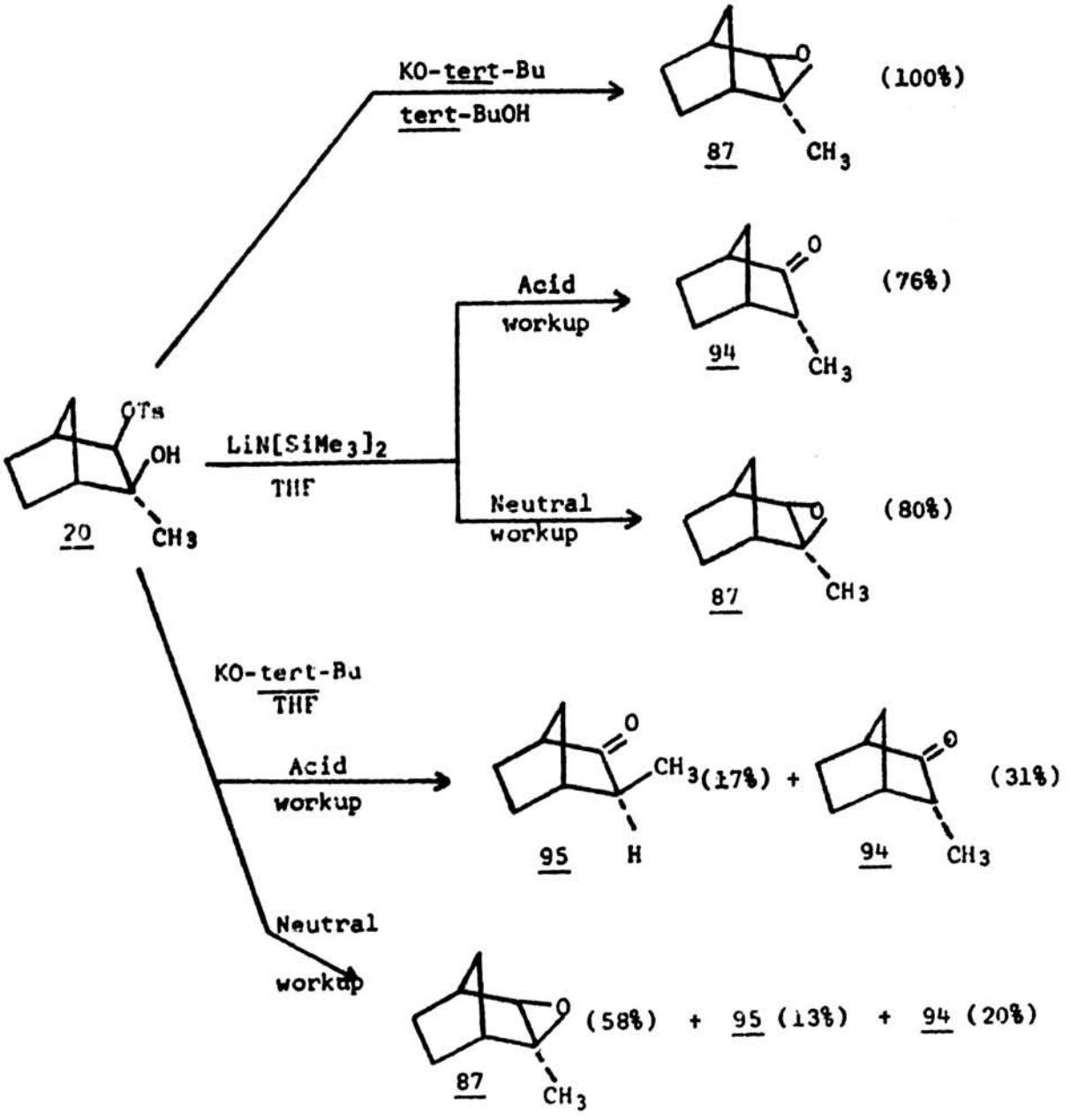
81 93 94 95

Knowing that epoxides are generally susceptible to acidic media, treatment of epoxide 87 with the acidic workup conditions led to complete consumption of the epoxide with the formation of three new compounds that were not identified, but surprisingly, ketones 94 and 95 were not present. These results led us to believe that if epoxide 87 was initially formed from tosylate 20 then it was being destroyed by the acid workup.

It was found that by using a modified workup to eliminate acidic conditions, epoxide 87 was indeed being formed from tosylate 20.

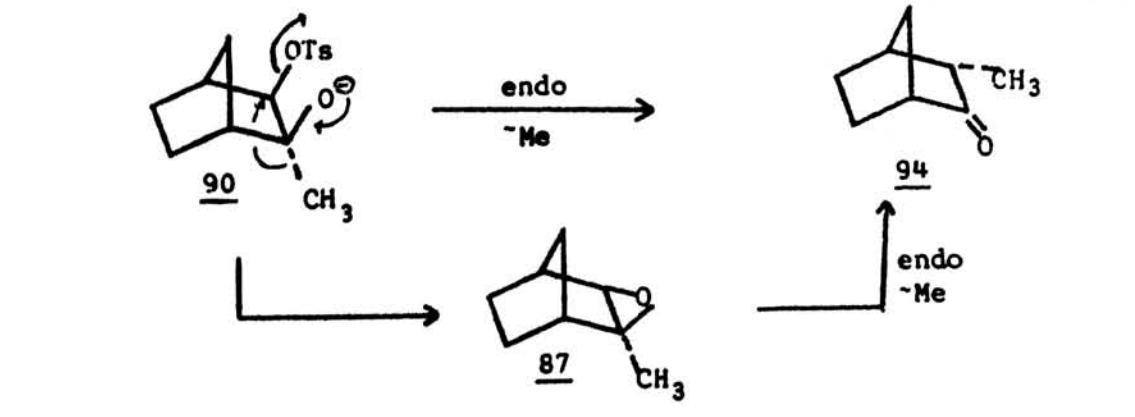
For example, with lithium bis(trimethylsilyl)amide as the base a mixture was obtained that was shown to consist of 80% epoxide 87 along with two unidentified components. However, when tosylate 20 was allowed to react with potassium tert-butoxide five products were obtained. Vpc analysis showed the material to consist of epoxide 87 (58%), ketone 95 (13%) and ketone 94 (20%) along with two unidentified products. The combined results are depicted in Scheme VI.

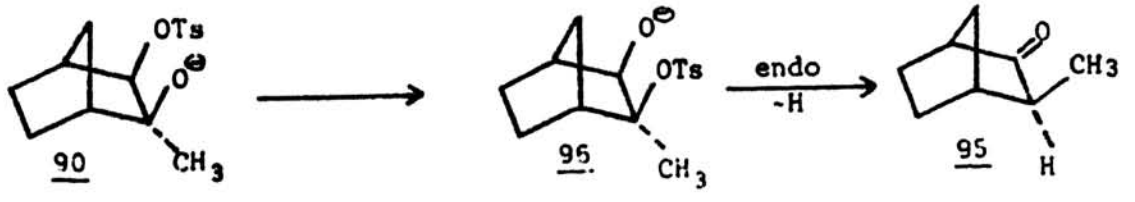
Scheme VI



As can be noted, the major isolated product from tosylate 20 is epoxide 87, when it is not destroyed by the acidic workup, with the reaction with potassium tert-butoxide in tetrahydrofuran being the only one producing other products in significant amounts. From these results we concluded that epoxide 87 was being formed from tosylate 20, but was being destroyed during the acidic workup. However, the results are quite puzzling because one would expect the same products from the acidic destruction of epoxide 87 no matter what base was initially used. It is possible that the cation present ($K^{\oplus}$ or $Li^{\oplus}$) in the acidic solution influences what products will be formed.

The formation of endo-ketone 94 can be explained by two different pathways. One would involve the direct formation of ketone 94 via an endo-methyl migration of the initially formed anion. The other pathway would involve a two step sequence in which the initially formed anion gives epoxide 87, which rearranges by an endo-methyl migration to give ketone 94.





The formation of exo-ketone 95 is not so straightforward because inversion of configuration has occured at the carbon bearing the methyl group. Undoubtedly the reaction conditions are basic enough to cause interconversion between ketones 94 and 95, but the isomer ratio observed here is not the same as that observed under equilibration conditions (see Experimental section). The formation of exo-ketone 95 could be explained by a mechanism in which the initially formed anion 90 undergoes transtosylation to give a new anion 96 which could then collapse by endo-hydride migration to give ketone 95 with inversion of configuration.

If these are the mechanisms for the formation of ketones 94 and 95, the endo-methyl and endo-hydride migrations represent a very unique rearrangement in the norbornyl system. We believe that these observations represent one of the first cases of an endo-endo hydride and methyl migration in a norbornyl system in which the reaction is initiated by base.[72]

From studies done on the bicyclo[2.2.1]heptane system,[74] it has been found that hydrogen and alkyl groups are extremely reluctant to migrate in a 2,3-endo fashion. An explanation based on torsional effects[74a] has been advanced to account for these observations. It appears that the torsional effects are strong enough to force endo-hydrogens or alkyl groups to become exo through circuitous routes before they can migrate to the adjacent position. Until just recently, the cationic analog of an endo-endo hydride migration[75] to a secondary carbonium ion was an unknown occurance.

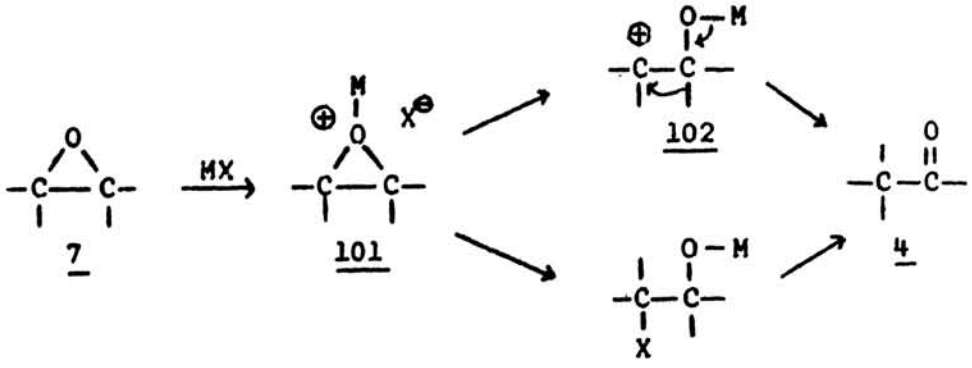
As can be seen from the above results, our hopes of a synthetic entry into the bicyclo[2.1.1]hexane system were not realized by the basic rearrangement of tosylate 20. However, the reaction of tosylate 20 with

potassium tert-butoxide did present an interesting question. What course of reaction would epoxide 87 take in the presence of an acid?

The reaction of epoxides with acids and Lewis acids to form carbonyl compounds has been known for many years. Lewis and Hendrick[76] have shown that α-pinene oxide (97) rearranges to give aldehyde 98 upon treatment with zinc bromide. The driving force of the reaction appears to be the relief of ring strain. Norbornene oxide (99) was found to undergo a similar transformation[9a] when treated with lithium perchlorate.

97 98 99 100 (83%) 82 (17%)

From studies done on the epoxide rearrangement, the products obtained were found to be dependent on the nature of the starting epoxide and the catalyst used.[77] Two mechanisms have been advanced for the rearrangement of epoxides in the presence of Lewis acids.

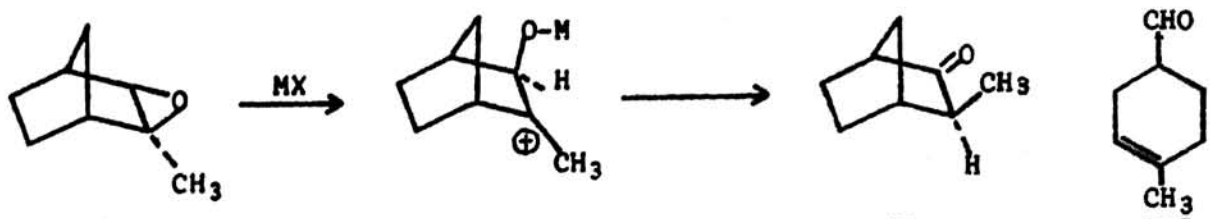


7 101 102 4 103

Both involve the initial formation of complex 101 with subsequent epoxide opening by either of two paths. One involves the formation of a carbonium

ion 102, which can undergo rearrangement to give aldehyde or ketone products 4. The other pathway available for complex 101 involves formation of halohydrin salt 103 by anion assisted opening of the epoxide ring. The halohydrin salt 103 can then undergo a similar rearrangement to give carbonyl product 4.

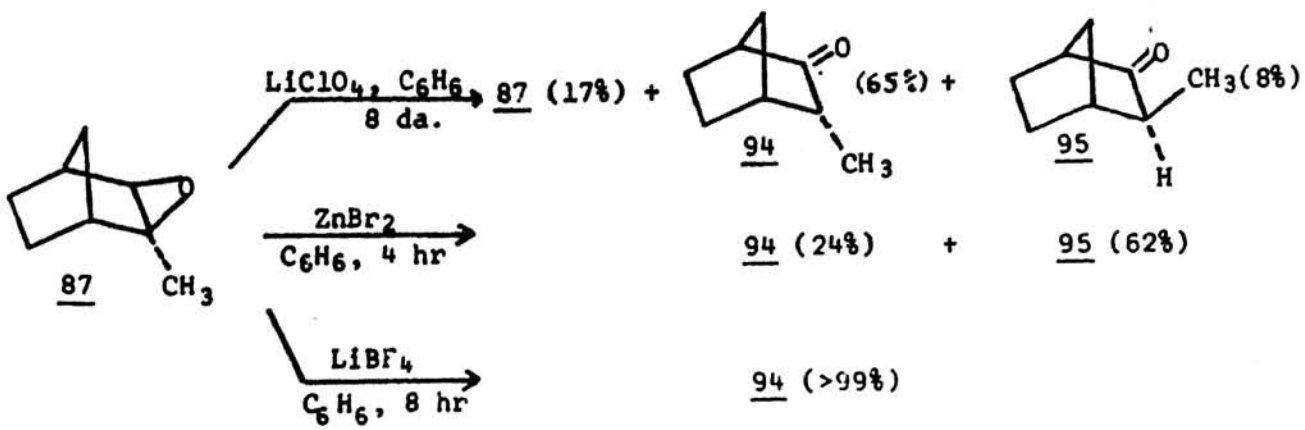
Rickborn and Gerkin[9a] have shown from kinetic data and product distribution studies that with lithium perchlorate in benzene the free carbonium ion pathway is favored for trisubstituted epoxides. With lithium bromide the halohydrin pathway is operative. If this is the case then epoxide 87 would be expected to rearrange, when treated with lithium perchlorate, in such a manner as to give the more stable carbonium ion 104, which could then undergo endo-hydride migration to give ketone 95. It is possible that some skeletal rearrangement could occur to give al-



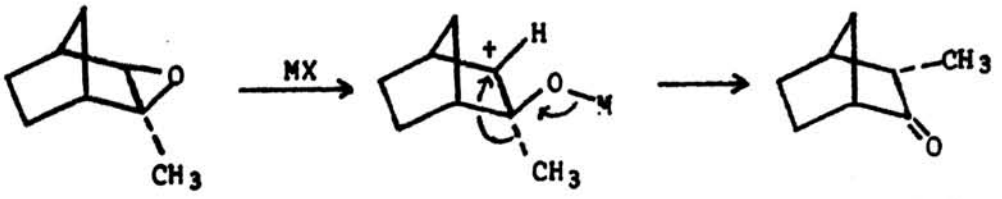
87 104 95 105

dehyde product 105 (cf. rearrangement of epoxides 97 and 99). The behavior of epoxide 87 towards the Lewis acids zinc bromide, lithium perchlorate and lithium tetrafluoroborate was studied. The results of these rearrangements are shown in Scheme VII.

Scheme VII



The results with lithium perchlorate are somewhat surprising in that complete reaction never occured even after extended reaction times, whereas, in the reported study,[9a] trisubstituted epoxides reacted fairly rapidly. Also to be noted is that with lithium perchlorate epoxide 87 did not give ketone 95 as the major product as was predicted by the proposed mechanism.[9a] The formation of ketone 94 requires that a somewhat different mechanism be followed. Its formation indicates that the epoxide opens to give the less stable carbonium ion intermediate 106, which then undergoes an endo-methyl migration.



87 106 94

The reaction of epoxide 87 with lithium tetrafluoroborate indicates that the mechanism proposed by Rickborn and Gerkin[9a] is inoperative. Here again, the observed product suggests that epoxide 87 opens in such a manner to give the less stable carbonium ion intermediate.

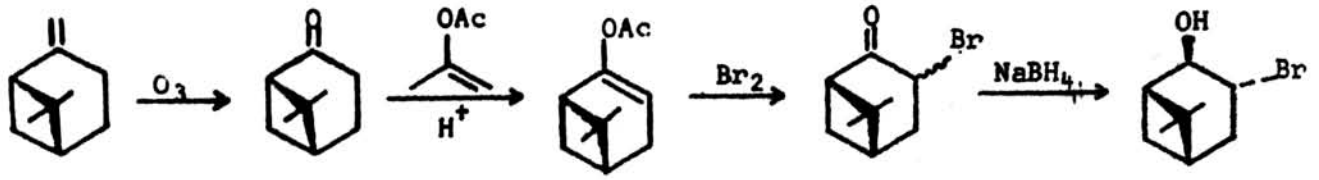
The reaction catalyzed by zinc bromide is the only one in which the major pathway is opening of the epoxide to give the more stable carbonium ion intermediate 104. However, a considerable amount of the epoxide must open in the opposite direction to account for the formation of ketone 94. Ketone 94 did not arise from isomerization of ketone 95 because it was found that both ketones were stable to the reaction conditions employed.

In these epoxide rearrangements, if it is true that an endo-hydride and an endo-methyl migration are occuring then these rearrangements also represent a unique transformation in the norbornyl system.[75]

Synthesis and Rearrangement of Bromohydrin 35

In the pursuit of synthetic entries into the bicyclo[2.1.1]hexane system via a semi-pinacol rearrangement, our next objective was to test the suitability of bromohydrin 35 as a precursor to this bicyclic system. Bromohydrin 35 appeared to be a logical choice for two reasons: (a) the bromohydrin should be easily prepared from readily available starting material and (b) Curtin and Harder[22] have shown that certain bromohydrins undergo ring contractions when treated with a base or silver oxide.

The synthesis of bromohydrin 35 is presented in the following scheme. Exhaustive ozonolysis[78] of β-pinene afforded nopinone (108) in moderate

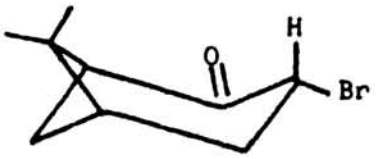


107 108 109 110(a) α-Br (b) β-Br 35

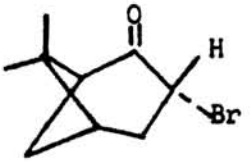
yield. Coxon and coworkers[79] have reported that treatment of enol acetate 109 under select conditions affords either bromoketone 110a or 110b free from the other isomer. To take advantage of this, nopinone (108) was converted to enol acetate 109 by treatment with isopropenyl acetate and a catalytic amount of p-toluenesulfonic acid.[79] Enol acetate 109 was then subjected to the reaction conditions described by Coxon et al.[79] In our hands, large scale reaction provided only one isomer that had properties reported by Coxon and coworkers[79] for bromoketone 110a.

The structure of bromoketone 110a has been determined by X-ray crystallography[80] and the compound has been shown to possess conformation 111a in which the bromine atom occupies an equitorial position in the solid phase. Ketone 110a has also been characterized by observing the

H-3 nmr resonance. The observed large coupling constants for the proton in the CHBr group with adjacent protons led Grimshaw and coworkers[81] to



111a



111b

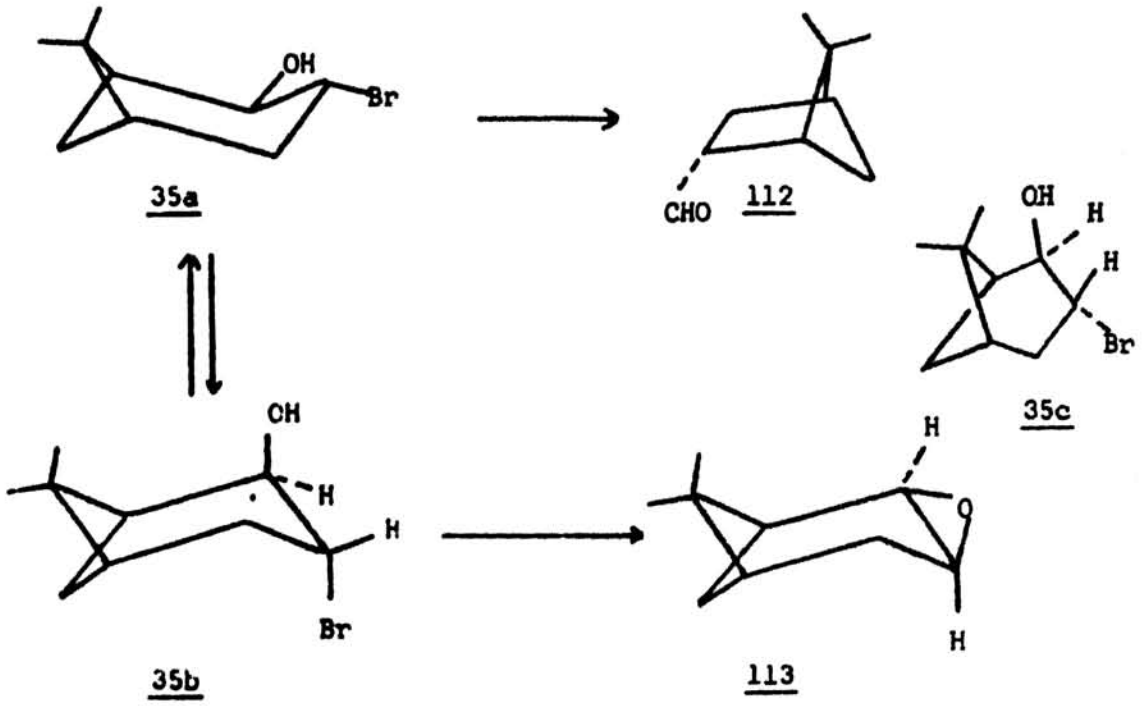
suggest that in solution, as in the solid phase, the bromoketone 110a exists to a considerable extent in the conformation $CH_{ax}Br_{eq}$. Coxon and coworkers[79] interpreted these results as an indication that in ketone 110a the ring carbon atoms 1-5 are essentially coplanar as represented in 111b.

A further indication that the bromoketone we isolated was assigned the correct structure was that isomerization[81] of the isolated ketone with sodium methoxide in methanol afforded a new ketone, to the extent of 83%, that had spectral properties reported for ketone 110b.[79] The equilibrium ratio obtained here was the same as reported by Grimshaw et al.[81]

Treatment of ketone 110a with sodium borohydride afforded a viscous liquid in 77% yield that was shown by vpc analysis to be 92% pure with a single impurity. Based on the assumption that reduction will occur from the least hindered side, structure 35 was assigned to this material.

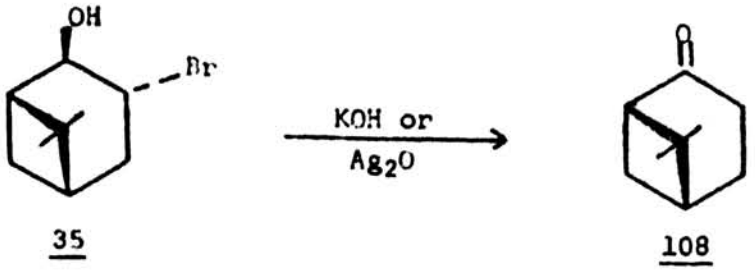
Depending on which conformation the transition state resembles, one can predict with reasonable certainty what products are possible from the action of potassium hydroxide or silver oxide on halohydrin 35. If the reactive conformer is 35a, one would expect aldehyde 112 because the C-1--C-6 bond and the bromine group are trans and coplanar. As was noted previously, this alignment of groups represents the optimum conditions

for backside displacement,[22] hence, ring contraction would be expected to occur. If the transition state resembles the conformation depicted by 35b in which the hydroxyl and bromine groups are trans and diaxial, then epoxide formation would be the ideal pathway to follow.[22] It is entirely possible that the transition state resembles a conformation that lies somewhere between the two extremes, for example 35c, and one would expect to get a mixture of products 112 and 113.

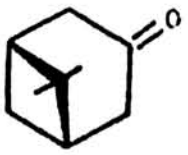


When halohydrin 35 was treated under the reaction conditions described by Curtin and Harder[22] none of the expected products were obtained. Instead, bromohydrin 35 gave nopinone (108) as the only product when treated with either potassium hydroxide or silver oxide. In either case, the formation of nopinone (108) can be explained by a sequence of dehydrohalogenation[22] to form an enolate anion, in the case of potassium hydroxide, or enol when silver oxide is used and then tautomerization (and protonation in the case of potassium hydroxide) to give the observed

product.



35 108



114

The possibility that an epoxide intermediate was formed and then subsequent rearrangement can be discredited, but not eliminated, in two ways: (a) the reaction conditions used were the same as those described[22] in which no problems were encountered for epoxide isolation and (b) the rearrangement of an epoxide intermediate would surely give a mixture of products consisting of nopinone (108) and ketone 114.

Since this bromohydrin failed to provide a synthetic entry into the bicyclo[2.1.1]hexane system our attention was directed towards a more pressing problem.

A New Route to Bicyclo[2.1.1]hexenes

The bicyclo[2.1.1]hexene system has proven to be very elusive from a synthetic point of view. The additional strain introduced by the carbon-carbon double bond, in an already strained system, makes it a challenging goal in any synthetic scheme. The schemes attempted so far have been directed toward the concept of introducing the double bond into a preexisting bicyclo[2.1.1]hexane system (i.e. eq. 6).[48b,54,55]

(6)

78

(7)

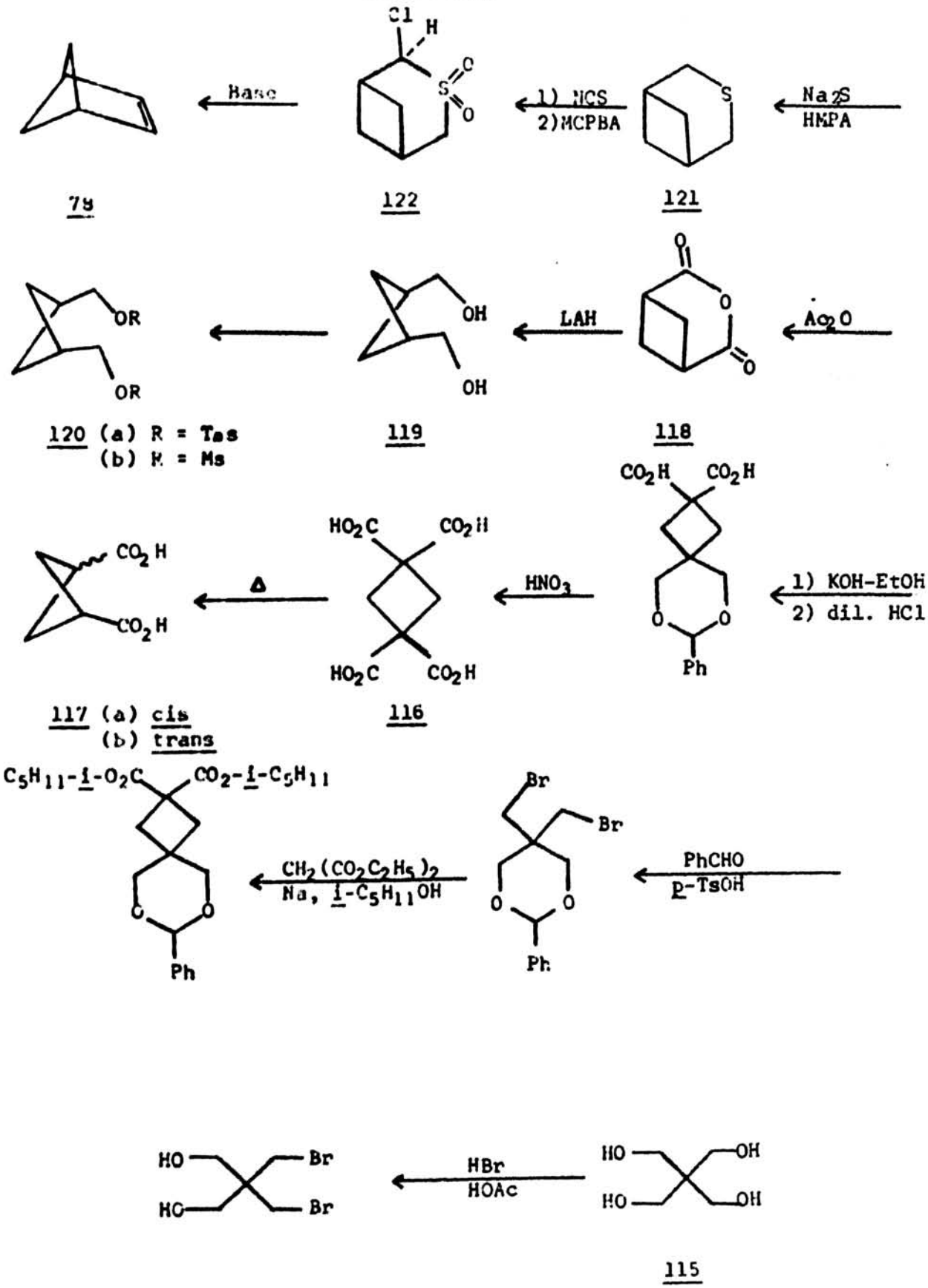
78

Instead of starting with the bicyclo[2.1.1]hexane system, we thought it might be possible to generate the double bond and the desired bicyclic ring system in a single operation (i.e. eq. 7). This would involve the extrusion of X with formation of two bonds between the carbon atoms formerly attached to X.

A method which accomplishes this type of transformation is the Ramberg-Bäcklund reaction,[28] which involves the extrusion of sulfur dioxide, similar to that depicted in eq. 7. The Ramberg-Bäcklund reaction has been used to form various propellene systems[46,82] in which considerable strain is present.

The precursor α- halosulfone required for the synthesis of bicyclo[2.1.1]hexene (78) is that shown by structure 122. A search of the literature revealed that sulfone 122 had not been prepared. Based on developed procedures for preparing cyclobutane diacids[83] and for the conversion of diacids to α-halosulfones,[46,82] the proposed synthetic scheme for preparing olefin 78 is illustrated in Scheme VIII.

Scheme VIII



79 122 121

120 (a) R = Tos
(b) R = Ms

119 118

117 (a) cis
(b) trans

116

115

Following the procedure of Allinger and Tushaus,[83] with some slight modifications, tetra-acid 116 was obtained in workable quantities, starting with pentaerythritol (115).

The thermal decarboxylation of tetra-acid 116 has been reported [83] to yield a mixture of cis-diacid 117a and trans-diacid 117b. The cis-diacid was found to react preferentially with acetyl chloride to form cyclic anhydride 118, which could be separated from trans-diacid 117b to give both compounds in pure form after sublimation. This procedure[83] afforded cyclic anhydride 118 in 45% crude yield free from trans-diacid 117b. This indicated that a substantial amount of equilibration between the cis and trans-diacids is not occuring during anhydride formation. The trans-diacid could be equilibrated and then recycled to produce more cyclic anhydride 118.

To circumvent this process of recycling the trans acid, appropriate reaction conditions were sought that would epimerize the trans acid to this cis isomer during anhydride formation. It was found that when acetic anhydride[84] was used, instead of acetyl chloride, the mixture of cis and trans acids, from thermal decarboxylation, afforded anhydride 118 in 93% yield.

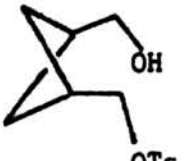
The formation of cyclic anhydride 118 serves a two-fold purpose. First, the required cis stereochemistry needed in all the intermediates throughout the rest of the scheme is introduced at this point. Secondly, this anhydride formation, free from any trans acid, eliminates a possibly difficult separation of the desired cis product from extraneous material that would surely be formed if subsequent transformations were done on a mixture of anhydride 118 and trans-diacid 117b.

Lithium aluminum hydride reduction of anhydride 118 afforded cis-diol 119, which could be converted to the ditosylate or dimesylate deri-

vative, 120a or 120b, respectively. Treatment[83] of a pyridine solution of cis-diol 119 with p-toluenesulfonyl chloride afforded a three component mixture, out of which ditosylate 120a was isolated in meager yields, along with component A, as a colorless liquid, and component B, the major constituent, as a colorless oil.

The spectral features of component A (see Experimental section) suggested that this compound was cyclic ether 123. However, the combustion analysis of component A did not support this assignment because the carbon content was found to be much lower than would be calculated from the formula for cyclic ether 123. The mass spectrum of component A showed prominant peaks at m/e values greater than 98, which also argues against this structural assignment.

123



124

Spectral features indicated that component B was monotosylate 124 (see Experimental section). This assignment was not supported by the following observations: (1) Shaking the sample with deuterium oxide produced no observable change in the nmr spectrum; (2) Treatment of component B with chromium trioxide-dipyridine complex[85] did not give any carbonyl product; and (3) Attempted tosylation[83] as before led to recovery of starting material.

Treatment of a methylene chloride solution of cis-diol 119 with methanesulfonyl chloride and pyridine afforded dimesylate 120b in good yield. Subsequent conversion to cyclic sulfide 121 could be difficult due to the sterically hindered nature of the reaction sites. Paquette

et al.[86] have found that in similar types of systems, the use of dry hexamethylphosphoramide (HMPA) was essential to the success of this Sn-2 displacement-cyclization. They[86] attribute this success to the high cation solvating capacity of HMPA, which greatly reduces the effective size of the nucleophile relative to its bulk in other media. This enables the nucleophile to approach the hindered center more easily because the steric repulsion of the system has effectively been diminished. Thus, treatment of dimesylate 120b in the described manner[86] afforded, in 54% isolated yield, cyclic sulfide 121 as a volatile, white solid, which was converted to α-chloro sulfone 122 by sequential treatment with N-chlorosuccinimide[86] and m-chloroperbenzoic acid.

The choice of base and solvent system for the Ramberg-Bäcklund reaction was a difficult one to make. The base must possess enough steric bulk to retard ether formation by nucleophilic displacement of the chloride, but the bulkiness must be kept within reason due to the steric crowding around the α'-hydrogen in the bicyclic system.

In regard to the solvent system, the solvent of choice must permit easy isolation of the olefin free from solvent. From preliminary practice runs to develop product isolation techniques using cyclohexene as a model compound, it was found that a vacuum transfer isolation procedure was the most promising. Hence, the desired solvent must have a high boiling point.

With these requirements in mind for the base and the solvent to be used, a search of the literature revealed that Corey and Block[87] had developed a procedure that appeared to be ideal for our system. Their procedure used tert-amyl alkoxide (tert-amyl alcohol in the presence of a large excess of sodium hydride) as the base and tetraglyme as the solvent. This base-solvent system allowed the olefin to be isolated

by vacuum transfer from the reaction mixture into a liquid nitrogen cooled trap. Due to the inaccesibility of tetraglyme, we used diphenyl ether as the solvent.

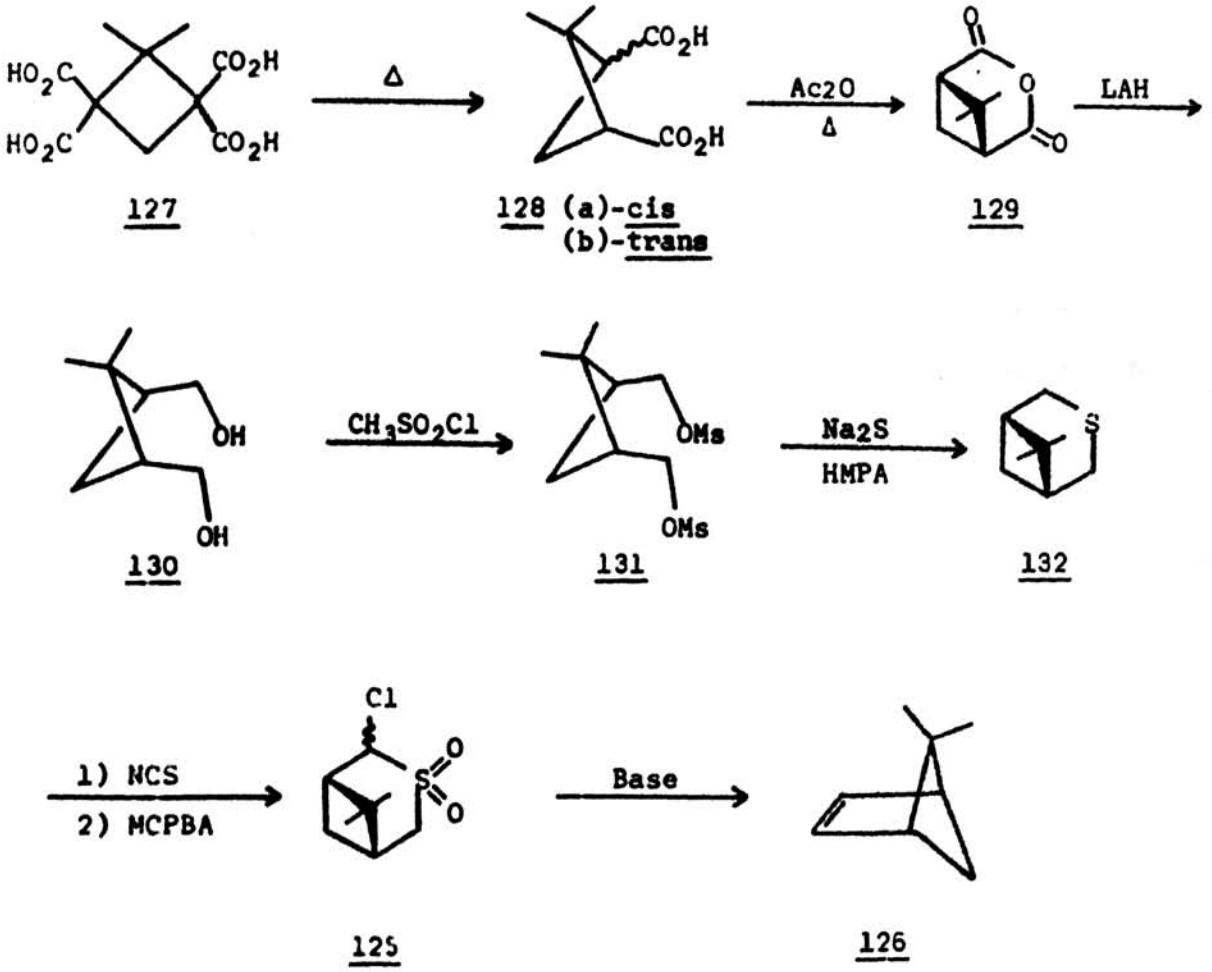
Using a slight modification of the reported procedure,[87] α-chloro-sulfone 122 afforded, in 69% yield, a clear liquid that was shown by vpc analysis to be 100% pure. The nmr spectrum of this liquid showed absorptions in the regions of δ6.80 (m), 2.53 (m), and 2.26 (m) with integration ratios of 2:4:2, respectively. The signal at δ6.80 is indicative of a strained carbon-carbon double bond hydrogen. These observations and the similarity of our spectral data to the reported data[55] confirm that the Ramberg-Bäcklund reaction did indeed give olefin 78 in high purity and good yield.

To investigate the generality of the Ramberg-Bäcklund reaction as a synthetic entry into the bicyclo[2.1.1]hexene system, a synthesis of α-chloro sulfone 125 was required so that subsequent treatment with base might afford olefin 126. Following the route described in Scheme VIII, tetra-acid 127,[88] which was generously given to us at the outset of this investigation, was converted to α-chloro sulfone 125.(Scheme IX).

Treatment of α-chloro sulfone 125 in the previously described manner afforded, in 40% yield, a clear liquid that was contaminated to the extent of 3%, with tert-amyl alcohol. The material was subsequently purified by preparative gas chromatography. The nmr spectrum showed absorptions in the regions of δ6.63 (t, J = 2 Hz), 3.00 (m), 2.27 (dd, J = 2 and 6 Hz), 2.02 (d, J = 6 Hz), 1.52 (s), and 1.03 (s) with integration ratios of 2:1:2:1:3:3, respectively. The absorption at δ6.63 is indicative of a hydrogen on a strained carbon-carbon double bond. The ir spectrum showed olefinic absorptions at 3110, 3070, 3040, 705, and

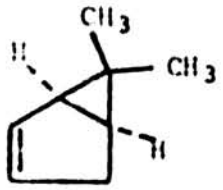
610 cm^{-1}. We feel that this data confirms that the Ramberg-Bäcklund reaction did give olefin 126 in high purity and workable yields.

Scheme IX

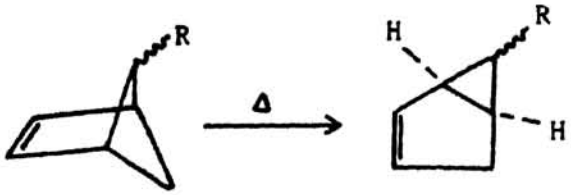


127 128 (a)-cis (b)-trans 129 130 131 132 125 126

A further note of confirmation that our structural assignment was correct is that the nmr sample of 126, when heated at 100° for 2 hr in a sealed tube, gave a new compound with spectral features similar to those reported for 133.[89a] This thermal rearrangement is not surprising because compounds of general structure 134 have been shown to undergo thermal rearrangement[89b] to give the corresponding bicyclo[3.1.0]hexene with great ease.



133



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From the results of these two Ramberg-Bäcklund reactions, we feel that a general route to the bicyclo[2.1.1]hexene system has been provided. Therefore, if the corresponding α-halosulfone can be prepared, then subsequent treatment with the appropriate base and solvent system should afford the corresponding bicyclo[2.1.1]hexene derivative.

EXPERIMENTAL

General Information.-- All melting points were determined in open capillary tubes using a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on either a Beckman IR-8 or AccuLab-3 spectrophotometer. Nuclear magnetic resonance spectra were determined with a Varian T-60, A-60, A-60-A, or HA-100 nuclear magnetic resonance spectrometer with tetramethylsilane as the internal reference. An Aeorgraph A-90-P, Bendix model 2300, or F & M model 700 gas chromatograph with thermal conductivity detectors were used for analytical vapor phase chromatography. The traces were registered on either a Beckman Ten-Inch flatbed or a Honeywell Electronik model 194 Ten-Inch recorder, both fitted with a disc integrator. The columns used for the analysis gave the best separation of peaks of all columns attempted. Mass spectra and exact molecular weight determinations were obtained on a Varian MAT CH-5 spectrometer. Microanalyses were obtained using a Hewlett-Packard model 185-B Carbon Hydrogen Nitrogen Analyzer.

2-Methylnorbornene (81).[66] -- Methylcyclopentadiene dimer[90] (241.4 g) and sodium carbonate (7.10 g) were placed in a 1 l Magne Dash Autoclave. The bomb was charged with ethylene to a pressure of 900 p.s.i. and heated for 7 hr at 190°. On cooling, the contents of the bomb were filtered and distilled; the portion which distilled between 100 and 120° was collected to give 81.20 g of clear liquid. Annular distillation of a portion of this sample to remove the 1-methylnorbornene followed by short path distillation of the pot residue gave 2-methylnorbornene (81); b.p. 116.5° (lit.[66] 118°); ir(CCl_4) 2950, 2890, 1640, and 1440 cm^{-1}; nmr(CCl_4)δ 5.45 (b.s., 1), 2.75 (b.s., 1), 2.60 (b.s., 1), 1.70 (d, 3, J = 2.0 Hz) and

1.65-0.80 (m, 6).

2-endo-Methyl-2,3-cis,exo-norbornanediol (80).[70] -- A solution of 23.40 g (0.148 mol) of potassium permanganate and 5.0 g of sodium hydroxide in 800 ml of water cooled to 0° was added quickly, with vigorous stirring, to a cold (-7°) mixture of 1.0 l of tert-butyl alcohol, 200 ml of water and 500 g of cracked ice containing 10.82 g (0.100 mol) of olefin 81. After 3.0 min sulfur dioxide was bubbled through the solution to ensure complete reduction of the permanganate. The precipitate of manganese dioxide was removed by filtration through a layer of Super-cell. The filtrate was evaporated on the steambath under reduced pressure to ca 250 ml and was continuously extracted with ether for 48 hr. Concentration of the ether layer afforded 7.22 g (51%) of clear, viscous oil. This oil was chromatographed over 400 g of CC-7, 100-200 mesh silica gel contained in a 80 cm x 40 mm glass column. Elution with 50% ether in Skelly-B afforded 6.47 g (45%) of diol 80 as a sticky white solid: sublimed 34-36° (0.02-0.04 mm); m.p. 135.5-137.5° (lit.[72d] 126-128°); ir(CCl_4) 3400, 2980, 1380, 1050, 1030, and 930 cm^{-1}; nmr(CCl_4)δ 4.25 (d, 1, J = 5 Hz, CH-OH), 3.95 (s, 1, C-OH), 3.18 (unresolved d, 1, CH-OH), 2.0-0.9 (m, 11) with methyl singlet at 1.20.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.41; H, 9.74.

2-endo-Methyl-2,3-cis,exo-norbornanediol 3-p-Toluenesulfonate (20).-- To a stirred solution of 0.284 g (2.00 mmol) of diol 80 in 3 ml of dry pyridine was added in one portion 0.573 g (3.00 mmol) of freshly recrystallized p-toluenesulfonyl chloride. After stirring for four days at room temperature, ca. 2.5 g of ice was added and stirred with the reaction mixture for 0.5 hr. The mixture was diluted with 110 ml of ether and washed

with 110 ml of water, twice with 110 ml portions of cold 5% hydrochloric acid, once with 110 ml of saturated sodium bicarbonate solution, and again with 75 ml of water. The ether layer was dried over magnesium sulfate and concentrated on the rotary evaporator to afford 0.587 g (99%) of clear viscous oil. Three recyrstallizations from Skelly-B/ether afforded 0.375 g (63%) of tosylate 20 as transparent plates: m.p. 66.5-67.5°; ir(CCl_4) 3600, 3540, 2970, 2880, 1605, 1385, 1345, 1200, 1185, 990, 915, and 865 cm^{-1}; nmr(CCl_4)δ 7.72 (d, 2, J = 8 Hz, aromatic), 7.26 (d, 2, J = 8 Hz, aromatic), 3.82 (s, 1, CH-OTs), 2.52 (s, 1, C-OH), 2.40 (s, 3, Ar-CH_3), and 1.14 (s, 3, CH_3-C-OH).

Anal. Calcd for $C_{15}H_{20}SO_4$: C, 60.80; H, 6.80. Found: C, 60.50; H, 6.89.

Treatment of 2-endo-Methyl-2,3-cis,exo-norbornanediol 3-p-Toluenesulfonate (20) with Base. -- (A). Treatment of tosylate 20 with potassium tert-butoxide in tert-butyl alcohol. - To a stirred solution of 1.90 g (16.90 mmol) of potassium tert-butoxide in 150 ml of dry tert-butyl alcohol at 65° under nitrogen was added a solution of 2.692 g (9.085 mmol) of tosylate 20 dissolved in 50 ml of dry tert-butyl alcohol. The reaction mixture was stirred for 10 hr at 65° and then allowed to stand overnight at room temperature. The reaction mixture was concentrated to ca. 75 ml by distillation at a slightly reduced pressure and keeping the pot temperature at less than 100°. The flask and contents were cooled, diluted with water and then thoroughly extracted with ether. The combined ethereal extracts were washed with water, brine and dried over anhydrous magnesium sulfate. The ether was removed by distillation at atmospheric pressure and the residue was heated (170 mm) to remove the tert-butyl alcohol to afford 0.949 g (84%) of clear liquid. Vpc analysis using a 6' x ¼" column

packed with 15% PPGA on 60/80 Chrom W support showed the material to consist of tert-butyl alcohol (25%) and 2-endo-methyl-2,3-exo-epoxynorbornane (87) (75%). This corresponds to a 63% isolated yield of vpc volatile product. Preparative vpc using a 6' x ¼" column packed with 15% Dow-710 on 60/80 ABS support gave sufficient material to obtain an ir spectrum that was identical to that of an authentic sample.

(B). Treatment of tosylate 20 with potassium tert-butoxide in tetrahydrofuran. - Following the procedure described in part A using 159 mg (1.42 mmol) of potassium tert-butoxide in 6.0 ml of dry tetrahydrofuran and 281 mg (0.95 mmol) of tosylate 20 dissolved in 20 ml of dry tetrahydrofuran, the reaction was found to be complete after 1 hr at 65°. The reaction mixture was cooled, diluted with ca. 50 ml of ice-water and thoroughly extracted with ether. The organic extracts were washed with 50 ml portions of 2.5% cold hydrochloric acid, saturated sodium bicarbonate solution, water, brine and dried over sodium sulfate. Concentration by distillation at atmospheric pressure afforded 290 mg of liquid, which was shown by vpc[91] analysis to contain tetrahydrofuran, 3-exo-methylnorcamphor (95)[92] (17%), 3-endo-methylnorcamphor (94)[92] (31%), and four unknowns amounting to 52% of the mixture. The ir spectrum of the mixture showed predominant absorptions at 3400, 2950, 1745 and 1070 cm^{-1}.

(C). Neutral workup. - Following the procedure described in part B using 0.510 g (4.55 mmol) of potassium tert-butoxide in 18 ml of dry tetrahydrofuran and 0.910 g (3.08 mmol) of tosylate 20 in 60 ml of dry tetrahydrofuran, the reaction was found to be complete after 1 hr at 65°. The reaction mixture was cooled, diluted with water, saturated with sodium chloride and thoroughly extracted with ether. Drying over sodium sulfate and removal of as much of the solvent as possible by distillation at atmo-

spheric pressure afforded 1.150 g of liquid which was shown by vpc[91] analysis to contain tetrahydrofuran, 2-endo-methyl-2,3-exo-epoxynorbornane (87)[92] (58%), 3-exo-methylnorcamphor (95)[92] (13%), 3-endo-methylnorcamphor (94)[92] (20%), and two unknowns amounting to 9% of the mixture.

(D). Treatment of tosylate 20 with lithium bis(trimethylsilyl)-amide.[93] - In a flame dried three-necked 25 ml flask under nitrogen was placed 5.0 ml of dry tetrahydrofuran and 0.30 ml (0.234 g, 1.45 mmol) of hexamethyldisilazane. To this stirred solution was added 1.0 ml of 1.10 N methyllithium in ether at a rate of 1 drop per sec. The resulting mixture was stirred for 0.5 hr at 35°. The ether was removed by purging the flask with nitrogen and then replaced with 1.5 ml of dry tetrahydrofuran. To this stirred mixture heated to 35-40° was added dropwise a solution of 0.277 g (0.940 mmol) of tosylate 20 dissolved in 5 ml of dry tetrahydrofuran. The reaction mixture was heated at 40° for 22 hr, at 80° for 22 hr, and at 50° for 8 hr. The reaction mixture was cooled, diluted with water and thoroughly extracted with ether. The ethereal extracts were washed with 50 ml portions of cold 2.5% aqueous hydrochloric acid, saturated sodium bicarbonate solution, water, brine and dried over sodium sulfate. Concentration by distillation at atmospheric pressure afforded a liquid that was shown by vpc[91] analysis to consist of tetrahydrofuran, 3-endo-methylnorcamphor (94)[92] (76%), and 24% unknown material.

(E). Neutral workup. - Following the procedure described in part D using 2.10 g (13.0 mmol) of hexamethyldisilazane in 50 ml of dry tetrahydrofuran, 9.0 ml of 1.06 N methyllithium in ether and 2.423 g (8.20 mmol) of tosylate 20 in 50 ml of dry tetrahydrofuran, the reaction was stopped after 48 hr. The reaction mixture was cooled, diluted with 200 ml of ice-water and extracted with ether. The ethereal extracts were dried

over sodium sulfate and then distillation at atmospheric pressure afforded a sample that was shown by vpc[91] analysis to still contain solvent, but the products consisted of 2-endo-methyl-2,3-exo-epoxynorbornane (87)[92] and one unknown 21%.

3-endo-Methyl-2-exo-norbornanol (93). -- Following the procedure described by Zweifel and Brown[94] 5.40 g (0.05 mol) of 2-methylnorbornene (81) afforded 5.06 g (80%) of clear liquid which was sublimed at 40° (18 mm) to give 2.95 g (41%) of alcohol 93 as a transparent tacky solid: m.p. 90-93° (lit.[95] 95.5-97°); ir(CCl_4) 3650, 3350, and 1100-1000 cm^{-1}; nmr(CCl_4)δ 3.90 (b.s., 1, -OH) and unresolved absorption in the region of 2.2-0.8 with a methyl doublet at 0.95, J = 7 Hz.

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.34; H, 10.91.

3-endo-Methylbicyclo[2.2.1]heptan-2-one (94). -- To 0.50 g (3.96 mmol) of alcohol 93 in 50 ml of ether cooled to 0° was added 2.0 ml of 0.672 N chromic acid solution[96] over a period of 20 min. After addition was complete the reaction mixture was stirred for 5.5 hr at 0° and the ether layer was separated from the aqueous portion. The aqueous layer was saturated with sodium chloride and extracted with ether. The combined organic extracts were washed twice with 10 ml portions of saturated sodium bicarbonate solution, once with a 10 ml portion of water and dried over magnesium sulfate. Concentration on the rotary evaporator afforded 0.41 g (82%) of ketone 94 as a colorless liquid: ir(CCl_4) 1740 cm^{-1}; nmr(CCl_4)δ 0.96 (d, 3, $-CH_3$, J = 8 Hz). Vpc analysis[97] showed the material to consist of ketone 94 (85%), alcohol 93 (11%), and a trace of the isomeric ketone. The material was used without further purification.

Isomerization of Ketone 94 with Sodium Methoxide.[98] -- A solution of 205 mg (1.60 mmol) of ketone 94 in 3 ml of 3% sodium methoxide/methanol

was refluxed for 4 hr under nitrogen. The reaction mixture was cooled, treated with pentane and the phases were separated. The lower layer was saturated with sodium chloride and extracted twice with pentane. The combined pentane extracts were washed with brine and dried over magnesium sulfate. The pentane was removed by distillation through a 6-inch vigreaux column to afford a quantitative yield of a mixture of the two isomeric ketones. This mixture, on vapor phase chromatography,[99] was shown to consist of ketones 95 and 94 in a ratio of 1:1.7, respectively.

2-endo-Methyl-2,3-exo-epoxynorbornane (87).[71] -- To a three-necked 100 ml round bottom flask, fitted with a condenser, septum cap, nitrogen gas inlet, and a magnetic stirring bar, containing 40 ml of dry methylene chloride was added 4.778 g of 85% m-chloroperbenzoic acid. To this stirred slurry was added 2.230 g (20.6 mmol) of 2-methylnorbornene (81) dissolved in 20 ml of methylene chloride at such a rate to keep the temperature below 25°. After stirring for 5.5 hr the reaction mixture was filtered and the solid was washed several times with methylene chloride. The combined filtrates were shaken with a 10% sodium bisulfite solution until a negative starch-iodine test was obtained. The organic extracts were washed with saturated sodium bicarbonate solution, brine and dried over sodium sulfate. The solvent was removed by distillation at atmospheric pressure and distillation of the residue at reduced pressure afforded 1.778 g (70%) of epoxide 87 as a clear liquid: b.p. 70-72° (30 mm); ir(CCl_4) 2975, 2890, 1450, 1410, 1305, 1080, 940 and 890 cm^{-1}; nmr(CCl_4)δ 2.68 (b.s., 1, CH-O), 2.35 and 2.15 (each a b.s., 1 each, bridgehead protons), 1.80-1.0 (m, 9) with a methyl singlet at 1.33.

Reaction of Epoxide 87 with Zinc Bromide.[76b] -- A mixture of 0.150 g (1.20 mmol) of epoxide 87 and 30 mg of freshly fused zinc bromide in 5 ml

of reagent grade benzene was stirred at reflux for 2.0 hr under nitrogen and for an additional 2.5 hr at room temperature. The reaction mixture was diluted with ether, washed with water, saturated sodium bicarbonate solution, brine and dried over sodium sulfate. Concentration on the rotary evaporator afforded 0.115 g (77%) of slightly yellow liquid; ir(CCl_4) 3000, 2900, and 1750 cm^{-1}. Vpc analysis using a 6' x ¼" column packed with 15% PPGA on 60/80 Chrom W support showed the sample to consist of 3-exo-methylnorcamphor (95)[92] (62%), 3-endo-methylnorcamphor (94)[92] (24%), and 14% unknown material.

Reaction of Epoxide 87 with Lithium Perchlorate.[9a] -- A mixture of 0.198 g (1.60 mmol) of epoxide 87, 6 ml of reagent grade benzene, and 0.168 g (1.57 mmol) of lithium perchlorate was stirred at reflux for 8 days[100] under nitrogen. The reaction mixture was diluted with ether, washed with water, saturated sodium bicarbonate solution, brine and dried over sodium sulfate. Concentration on the rotary evaporator afforded 0.155 g (78%)[101] of yellow liquid, which was shown by vpc analysis[91] to consist of starting epoxide 87 (17%), ketone 95 (8%), ketone 94 (65%), and 10% of unknown material.

Reaction of Epoxide 87 with Lithium Tetrafluoroborate. -- A mixture of 0.270 g (2.18 mmol) of epoxide 87, 0.1155 g (1.11 mmol) of 90% lithium tetrafluoroborate, and 10 ml of reagent grade benzene was stirred at reflux for 8 hr[102] under nitrogen. The cooled reaction mixture was diluted with 40 ml of ether, washed with water, saturated sodium bicarbonate solution, brine and dried over sodium sulfate. Concentration on the rotary evaporator afforded 167 mg (62%) of liquid that was shown by vpc analysis[91] to consist of endo-ketone 94[92] in greater than 99% purity ir($CHCl_3$) 1740 cm^{-1}; nmr(CCl_4)δ 0.93 (d, 3, J = 6.5 Hz).[98]

Nopinone (108).[78] -- Exhaustive ozonolysis of 10.0 g (73.5 mmol) of β-pinene (107) ($[\alpha]_D^{26}$ -16.2° ($CHCl_3$), Aldrich) in absolute methanol followed by sodium iodide workup in the prescribed manner[78b] afforded 8.79 g (88%) of crude 108 as a yellow oil. Distillation in vacuo afforded 6.60 g (65%) of clear, colorless nopinone (108): b.p. 77-79° (6 mm); $[\alpha]_D^{26}$ +37.2 ($CHCl_3$) [lit.[78b] 83-86° (12 mm); $[\alpha]_D^{20}$ +35.6 (c 8, ethanol) from β-pinene $[\alpha]_D^{20}$ -18.8 (neat)]; ir(CCl_4) 2980, 1715, 1390, and 1375 cm^{-1}; nmr(CCl_4)δ 2.7-1.5 (m, 8), 1.33 (s, 3, CH_3), and 0.83 (s, 3, CH_3).

Enol Acetate of Nopinone, 109.[79] -- A solution of 30.0 g (0.218 mol) of nopinone (108) and p-toluenesulfonic acid (1.4 g) in 600 ml of isopropenyl acetate was heated to reflux and the acetone formed in the reaction was distilled from the system through a 12" column packed with silylated glass beads. After 19.5 hr, during which time 40 ml of distillate had been collected, the remaining isopropenyl acetate was removed under reduced pressure. The residue was diluted with 500 ml of ether, washed with water, and dried over potassium carbonate. Concentration on the rotary evaporator afforded 40.9 g (105%) of crude 109 as a red liquid. Distillation in vacuo afforded 35.4 g (91%) of 109 as a clear liquid: b.p. 91-93° (10 mm); $[\alpha]_D^{26}$ -18.4° (c 1.0; $CHCl_3$) [lit.[79] 72° (4.6 mm); $[\alpha]_D^{26}$ -18.6° (c 1.05; $CHCl_3$)]; ir(CCl_4) 1760 cm^{-1}; nmr(CCl_4)δ 5.10 (m, 1, olefinic proton), 2.65-2.0 (m, 6), 2.01 (s, 3, CH_3CO -), 1.32 (s, 3, CH_3) and 0.96 (s, 3, CH_3).

Bromination of Enol Acetate 109.[79] -- (A). -- A solution of 0.75 ml of bromine in 10 ml of carbon tetrachloride was added over a 35 min period to a stirred solution of 2.50 g (13.90 mmol) of enol acetate 109 in 12.5 ml of carbon tetrachloride at 0°. After stirring for an additional 5 min

the reaction mixture was diluted with 50 ml of ether and washed with 10 ml portions of brine until the washings were neutral. The ether layer was dried over sodium sulfate and concentrated on the rotary evaporator to afford 3.00 g (102%) of wet yellow solid: m.p. 46-60°; ir(CCl_4) 1730 cm^{-1}; nmr(CCl_4)δ 4.33 (dd, 1, J = 3 and 8 Hz, -CHBr), 2.9-2.1 (m, 6), 1.41 (s, 3, CH_3), and 0.87 (s, 3, CH_3). Recrystallization of the crude material from absolute methanol afforded 1.98 g (68%) of 3-α-bromonopinone (110a): m.p. 69-70.5°; $[\alpha]_D^{26}$ +153.2° (c 1.65; $CHCl_3$) [lit.[79] 69.5-70°; $[\alpha]_D^{23}$ +146 (c 1.05; $CHCl_3$)]; ir($CHCl_3$) 1730 cm^{-1}; nmr(CCl_4)δ 4.28 (dd, 1, J = 7 and 3.5 Hz, -CHBr), 2.9-2.2 (m, 6), 1.40 (s, 3, CH_3) and 0.83 (s, 3, CH_3).

(B). -- A solution of 0.75 ml of bromine in 10 ml of carbon tetrachloride was added over a 25 min period to a stirred suspension of anhydrous sodium carbonate (2.50 g) in a solution of 2.50 g (13.90 mmol) of enol acetate 109 in 10 ml of carbon tetrachloride at 0°. Workup as above afforded 3.17 g (108%) of wet yellow solid: ir and nmr identical to the crude material in part A above. Recrystallization of the crude material from absolute methanol afforded 1.73 g (59%) of material that was identical to 3-α-bromonopinone (110a) that was obtained above.

Isomerization of 3-α-bromonopinone (110a).[81] -- A solution of 100 mg (0.44 mmol) of ketone 110a and 50 mg of sodium methoxide in 2 ml of absolute methanol was stirred for 10 min at room temperature under nitrogen. The reaction mixture was diluted with 5 ml of water, extracted with ether and dried over sodium sulfate. Concentration on the rotary evaporator afforded 97 mg (97%) of white solid: m.p. 103-107°; ir(CCl_4) 1740 cm^{-1}; nmr(CCl_4)δ 4.73 (dd, 1, J = 11 and 8 Hz, -CHBr), 3.1-2.0 (m, 6), 1.40 (s, 3, CH_3) and 0.85 (s, 3, CH_3). The nmr spectrum[79] indicates that the

sample was solely ketone 110b, but vpc analysis[103] indicated that the 3-α-isomer 110a was present to the extent of 17%.

2-β-Hydroxy-3-α-bromopinane (35).[104] -- A mixture of 1.02 g (4.70 mmol) of bromoketone 110a, 0.61 g (16.0 mmol) of sodium borohydride and 75 ml of absolute ethanol was stirred at room temperature for 4 days. The reaction mixture was diluted with 25 ml of brine and extracted with ether. The ethereal extracts were dried over sodium sulfate and concentrated on the rotary evaporator to afford 788 mg (77%) of bromohydrin 35 as a viscous liquid. Analysis on tlc showed essentially one spot and vpc analysis[105] showed the material to be 92% pure with a single impurity: ir(CCl_4) 3500, 1385, and 1365 cm^{-1}; nmr(CCl_4)δ 5.0-4.0 (m, 2, -CHOH-CHBr-), 2.65-1.8 (m, 6), 1.23 (s, 3, $-CH_3$) and 1.10 (s, 3, $-CH_3$).

Treatment of Bromohydrin 35 with Potassium Hydroxide.[22] -- A solution of 229 mg (1.04 mmol) of bromohydrin 35 in 3 ml of isopropyl alcohol was added to 5 ml of a 5% solution of potassium hydroxide in isopropyl alcohol and stirred at 55° for 1.75 hr under nitrogen. The reaction mixture was diluted with 10 ml of water and extracted with ether. After the organic extracts were dried over sodium sulfate, concentration on the rotary evaporator afforded 72 mg (50%) of slightly yellow liquid. Analysis on the vpc[105] showed only one peak and the ir spectrum was identical to that of nopinone (108).

Treatment of Bromohydrin 35 with Silver Oxide.[22] -- To 2.0 g of silver nitrate in 20 ml of water was added with stirring 0.72 g of potassium hydroxide in water. After decantation the oxide was washed ten times with water, five times with acetone, five times with ether, and dried under a high vacuum. The above procedure gave ca. 1 g of silver oxide which was used immediately. A solution of 245 mg (1.12 mmol) of bromohydrin 35

in 25 ml of hexane and 656 mg of the above silver oxide were stirred at 75° for 1.75 hr under nitrogen. The reaction mixture was filtered and the silver salts were washed several times with hexane. The combined organic washes were shaken with sodium sulfate to remove any remaining traces of silver salts and concentrated on the rotary evaporator to afford 94 mg (60%) of slightly yellow liquid. Analysis on the vpc[105] showed only one peak and the ir spectrum was identical to that of nopinone (108).

cis-1,3-Cyclobutanedicarboxylic Acid Anhydride (118).[83] -- (A). -- 1,1,3,3-Cyclobutanetetracarboxylic acid (116)[83] (12.50 g, 53.90 mmol) was decarboxylated by heating in an oil bath at 220° for 15 min. The resultant dark brown oil was cooled to room temperature and 18.10 g of acetyl chloride was added and the resulting solution was refluxed for 23 hr under nitrogen. The excess acetyl chloride and acetic anhydride were removed in vacuo, and the black residue was distilled in a Kugelrohr distillation apparatus. Anhydride 118 (3.08 g, 45.5%) sublimed as a white solid at 120-125° (1 mm): m.p. 146-152°;[106] ir($CHCl_3$) 1825, 1805, 1770, and 910cm^{-1}; nmr($CDCl_3$)δ 3.33 (t, 2, J = 2.5 Hz) and 3.1-2.3 (m, 4).

(B). -- Tetra-acid 116 was decarboxylated by heating in an oil bath at 208° for 30 min. The resulting black oil, which solidified upon cooling to room temperature was broken up and boiled four times with 200 ml portions of ether and filtered. Concentration of the ethereal solutions afforded 7.41 g (88%) of a mixture of cis- and trans-1,3-cyclobutanedicarboxylic acid, 117a and 117b respectively, as a white solid: m.p. 114-147°; ir(KBr) 3600-2400 and 1700 cm^{-1}; nmr(Acetone-d_6)δ 10.13 (s), 3.6-3.0 (m) and 2.8-2.2 (m). The three peaks had integration ratios of 2:2:4, respectively. The mixture of cis- and trans-diacids and 30 ml of freshly distilled acetic anhydride were heated[84] in an oil bath

at 140° for 28 hr under nitrogen. After stirring for an additional 22 hr at room temperature the excess acetic anhydride and acetic acid were removed *in vacuo*. The resulting black semi-solid residue was distilled in a Kugelrohr apparatus at 125-130° (0.7-0.8 mm). Anhydride 118 (6.029 g, 92.5%) sublimed as a white solid: m.p. 152-155°;[106] ir($CHCl_3$) and nmr ($CDCl_3$) as reported above.

cis-1,3-Bis(hydroxymethyl)cyclobutane (119). -- A slurry of 5.45 g (0.146 mmol) of lithium aluminum hydride in 300 ml of dry ether was placed in a flame dried 1 l three-necked flask fitted with a dropping funnel, condenser and nitrogen inlet, and a true-bore stirrer. To this stirred slurry a solution of 5.94 g (47.4 mmol) of anhydride 118 dissolved in 130 ml of dry tetrahydrofuran was added over a period of 45 min. After addition was complete the reaction mixture was heated to reflux and stirred for 28 hr at which time the reaction mixture was cooled and the excess reducing agent was destroyed[108] by the dropwise addition of 5.45 ml of water, 5.45 ml of aqueous 15% sodium hydroxide and 16.35 ml of water. The resulting white suspension was stirred for 1 hr at room temperature and filtered. The aluminum salts were washed with ether and the combined organic solvents were dried over sodium sulfate and concentrated on the rotary evaporator to afford 5.36 g (97.6%) of cis-diol 119 as a yellowish viscous oil: ir($CHCl_3$) 3600, 3560-3200 cm^{-1}; nmr(Acetone-d_6)δ 4.03 (bs, 2, -OH), 3.48 (unresolved d, 4, $-CH_2OH$) and 2.7-1.4 (m, 8, ring protons). This material was used without further purification.

Attempted Tosylation of cis-diol 119.[83] -- To a cold solution of 10.00 g (52.3 mmol) of freshly recrystallized p-toluenesulfonyl chloride (m.p. 66-68°) in 30 ml of dry pyridine was added 2.61 g (22.5 mmol) of

cis-diol 119. The reaction mixture was allowed to slowly warm to room temperature and stirred for a total of 23 hr at which time the reaction mixture was diluted with ether and washed twice with 60 ml portions of cold aqueous 10% hydrochloric acid, once with 50 ml of water and dried over sodium sulfate. Concentration on the rotary evaporator afforded 3.95 g (41.5%) of slightly colored liquid. A tlc of the crude product indicated that two and possibly three different compounds were present. The crude product was chromatographed on 110.5 g of SilcAR CC-7 silica gel; elution with 20% ether in Skelly-B afforded 261 mg of component A. Further elution with 50% ether in Skelly-B afforded 1.848 g of component B as a clear liquid and 1.713 g of 120a was obtained as a white solid upon elution with higher percentages of ether in Skelly-B. Component A was distilled in a micro-distillation apparatus to afford 175 mg of clear liquid: b.p. ca. 85° (7 mm); ir($CHCl_3$) 2980, 2950, 2870, 1460, 1445, 1345, 1290, and 1270 cm^{-1}; nmr($CDCl_3$)δ showed absorptions in the regions of 3.47 (d, J = 7 Hz), 3.0-2.0 (m) and 1.9-1.6 (m) with integration ration of 4:4:2, respectively. The material was shown to be homogeneous by tlc and vpc.[109]

Anal. Found: C, 47.07; H, 6.28

Component B was homogeneous on tlc and showed the following spectral features: ir($CHCl_3$) 1600, 1370, 1195, 1180, 1105, and 920 cm^{-1}; nmr ($CDCl_3$)δ 7.55 (dd, J = 8 and 8 Hz), 3.95 (d, J = 5.5 Hz), 3.43 (d, J = 6.5 Hz), 2.85-1.3 (m) with a singlet at 2.43 with integration ratios of 4:2:2:10, respectively. Ditosylate 120a: m.p. 76-78° (lit.[83] 76.5 - 77.5°) had the following spectral features: ir($CHCl_3$) 3020, 1600, 1370, 1200, 1185, 1110, and 965 cm^{-1}; nmr($CDCl_3$)δ 7.57 (dd, 9, J = 8 and 8 Hz, aromatic), 3.88 (d, 4, J = 6 Hz, $-CH_2OTs$), 2.40 (s, 6, $-ArCH_3$) and 2.3-

1.2 (m, 5, ring protons).

Dimesylate of cis-1,3-Bis(hydroxymethyl)cyclobutane (120b).[110] -- A solution of 116 mg (1.00 mmol) of cis-diol 119 in 1.0 ml of methylene chloride and 0.20 ml of pyridine was cooled to 0° with an ice-bath and then 0.250 g (2.18 mmol) of freshly distilled methanesulfonyl chloride [b.p. 58-59° (16 mm)] was added in one portion. The reaction mixture was allowed to warm slowly to room temperature and stirred under nitrogen for 20.5 hr at which time it was washed into a separatory funnel with 20 ml of methylene chloride. This was washed once with 2 ml of cold aqueous 5% hydrochloric acid, twice with 2 ml portions of water and dried over sodium sulfate. Concentration on the rotary evaporator afforded 241 mg (89.6%) of dimesylate 120b as a white solid: m.p. 92-94° ir($CHCl_3$) 3020, 2980, 2940, 1370, 1345, 1180, 980, and 955 cm^{-1}; nmr (Acetone-d_6)δ 4.13 (d, 4, J = 6 Hz, $-CH_2OMs$), 3.03 (s, 6, $-SO_2CH_3$) and 2.95-1.6 (m, 6, ring protons).

Anal. Calcd for $C_8H_{16}O_6S_2$: C, 35.28; H, 5.92. Found: C, 35.12; H, 6.01

3-Thiabicyclo[3.1.1]heptane (121). -- Using the procedure described by Paquette et. al[86] 11.81 g (43.40 mmol) of dimesylate 120b was allowed to react with 30.10 g (125.40 mmol) of sodium sulfide nonahydrate for 40 hr. The reaction mixture was cooled, diluted with 1 l of brine and extracted with pentane. The combined pentane extracts were washed three times with 75 ml portions of water and dried over sodium sulfate. Most of the pentane was removed by distillation through a 20" vigreaux column, but could not be completely removed due to the highly volatile nature of the sulfide. The material was sublimed at 40-50° (140-150 mm) to give 2.65 g (53.5%) of sulfide 121 as a white tacky solid: m.p. 68-71.5°;

ir(CCl_4) 2970, 3930, 2850, 1440, 1430, 1240, 995, 855, and 655 cm^{-1}; nmr (CCl_4)δ 3.04 (d, 4, J = 2.5 Hz, $-CH_2SCH_2-$), 2.55 (m, 2), 2.16 (m, 2) and 1.70 (m, 2).

Anal. Calcd for $C_6H_{10}S$: mol. wt. 114.05032. Found(ms): 114.05015.

2-Chloro-3-thiabicyclo[3.1.1]heptane 3,3-Dioxide (122). -- Using the procedure described by Paquette et al[86] 836 mg (7.33 mmol) of sulfide 121 was allowed to react with 0.979 g of N-chlorosuccinimide in 20 ml of carbon tetrachloride. The reaction mixture was filtered and the solid was washed six times with 2 ml portions of carbon tetrachloride. The filtrate was cooled to 0° with an ice-bath and to this was added a solution of 3.09 g of 85% m-chloroperbenzoic acid in 18 ml of ether. After stirring for 24 hr the reaction mixture was washed into a separatory funnel with ether and washed three times with 20 ml portions of aqueous 1 M sodium hydroxide, twice with water, once with brine and dried over sodium sulfate. Concentration on the rotary evaporator afforded 868 mg (65.5%) of crude product that consisted of ca. 40% m-chloroperbenzoic acid and ca. 60% chlorosulfone 122.[111] An analytical sample of 122 was obtained by preparative tlc using a 20 x 20 cm x 100 μ Silplate-F-22 and eluting with benzene/ethylacetate (19:1): ir($CHCl_3$) 2960, 1330 and 1130 cm^{-1}; nmr($CDCl_3$)δ 5.10 (d, 1, J = 4 Hz, $-CHCl-SO_2-$), 3.67 (d, 2, J = 3.5 Hz, $-CH_2-SO_2-$) and 3.0-1.8 (m, 6, C-1, C-5, C-6, and C-7 protons).

Anal. Calcd for $C_6H_9SO_2Cl$: C, 39.89; H, 5.02. Found: C, 39.75; H, 5.13.

Bicyclo[2.1.1]hex-2-ene (78).[87] -- In a flame dried 100 ml three-necked round bottom flask equipped with a stirring bar, two stoppers and a condenser fitted with a 3-way stopcock, which provides a nitrogen inlet

and passage to a liquid nitrogen trap was placed 1.26 g of 56.8% sodium hydride dispersion in mineral oil. The sodium hydride was washed three times with Skelly-B and then 20 ml of freshly distilled diphenyl ether was added. The stirred suspension was heated to 70° and to this was added dropwise 0.62 g of tert-amyl alcohol (freshly distilled from calcium hydride). When hydrogen evolution ceased the system was evacuated to 0.2 mm for 30 min. The slurry was cooled to room temperature and 380 mg of crude chlorosulfone 122 dissolved in a small amount of diphenyl ether was added in one portion. The reaction mixture was placed under nitrogen and stirred vigorously for 1 hr at room temperature and then for 1 hr at 70°. After cooling to room temperature, the system was connected to the liquid nitrogen trap, via the 3-way stopcock, and evacuated to 0.1 mm. The temperature was gradually raised to 70° and kept at this temperature for 1 hr and 68.5 mg (68.5%) of olefin 78 was isolated as a clear liquid in the trap. Vpc analysis[103] showed the material to be 100% pure: ir(CCl_4) 3120, 3080, 3045, 2980, 2930, 2900, 2870, 1300, 1195, 845, and 675 cm^{-1}; nmr(CCl_4)δ[55] 6.80 (m, 2, olefinic hydrogen), 2.53 (m, 4, bridgehead and anti[112] -bridge protons), and 2.26 (m, 2, syn[112] -bridge protons).

Purification of 2,2-Dimethyl-1,1,3,3-cyclobutanetetracarboxylic Acid (127).[110] -- Decarboxylation of tetra-acid 127 was sensitive to small amounts of impurities. The following purification procedure circumvented these difficulties. To a well stirred solution of 32.40 g of tetra-acid 127 in 175 ml of acetone was added, over a period of 40 min, 250 ml of chloroform. After stirring for 0.5 hr at room temperature an additional 500 ml of chloroform was slowly added. The resulting mixture was cooled at 0° and the precipitate was collected and dried in an oven at 55°. Tetra-acid 127 was obtained in nearly quantitative yield

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Purification of 2,2-Dimethyl-1,1,3,3-cyclobutanetetracarboxylic Acid (127).[110] -- Decarboxylation of tetra-acid 127 was sensitive to small amounts of impurities. The following purification procedure circumvented these difficulties. To a well stirred solution of 32.40 g of tetra-acid 127 in 175 ml of acetone was added, over a period of 40 min, 250 ml of chloroform. After stirring for 0.5 hr at room temperature an additional 500 ml of chloroform was slowly added. The resulting mixture was cooled at 0° and the precipitate was collected and dried in an oven at 55°. Tetra-acid 127 was obtained in nearly quantitative yield

as a white solid: m.p. 195.5° dec (lit.[113] 200° dec.); nmr(Acetone-d_6)δ 9.22 (bs, 4, -CO_2H), 3.12 (s, 2, ring protons), and 1.43 (s, 6, 2-CH_3).

Norpinic Acid (128).[112] -- 14.30 g (53.80 mmol) of purified tetra-acid 127 was heated at 205° under nitrogen until bubbling ceased (0.75-1.0 hr). The yellow solid that was obtained upon cooling was dissolved in ether and filtered. Concentration on the rotary evaporator afforded 8.66 g (94%) of a mixture of cis and trans acids 128a and 128b: m.p. 121-135°; nmr(Acetone-d_6), the cis isomer exhibits two methyl singlets at 1.33 and 1.03 while the trans isomer gives a six hydrogen singlet 1.20δ. The cis isomer predominates in a ratio of ca. 1.6:1.

Norpinic Anhydride (129).[84] -- 3.00 g (17.4 mmol) of a mixture of cis and trans diacids 128a and 128b and 6.5 ml of freshly distilled acetic anhydride were refluxed under nitrogen for 16 hr. The excess acetic acid and acetic anhydride were removed in vacuo. The dark residue was cooled and a vacuum of 0.8 mm was applied to remove any traces of acetic acid or anhydride that may be present. The oily residue was taken up in ether, boiled with activated charcoal, and filtered. The residue that was obtained by concentration on the rotary evaporator was flash distilled, bulb-to-bulb [180° (0.20 mm)] to afford 1.64 g (61%) of slightly yellow solid. Recrystallization from ether gave 1.37 g (51%) of cyclic anhydride 129 as white square plates: m.p. 131.5-133° (lit.[84] 135°); ir($CHCl_3$) 1825 and 1770 cm^{-1}; nmr($CDCl_3$)δ 3.2-2.1 (m, 4, ring protons), 1.57 (s, 3, CH_3) and 1.25 (s- 3, -CH_3).

cis-1,3-Bis(hydroxymethyl)-2,2-Dimethylcyclobutane (130).[110] -- A slurry of 1.145 g (30.0 mmol) of lithium aluminum hydride in 120 ml of dry ether were placed in a flame dried 250 ml three-necked flask fitted with a true-bore stirrer, condenser, dropping funnel and a nitro-

gen inlet. To this stirred slurry a solution of 4.488 g (29.1 mmol) of norpinic anhydride (129) dissolved in 80 ml of dry ether was added over a period of 0.5 hr. After stirring for 2.5 hr at room temperature, an additional 1.27 g (33.4 mmol) of lithium aluminum hydride was added and the reaction mixture was refluxed for 21 hr under nitrogen. The cooled reaction mixture was treated[108] sequentially by the dropwise addition of 2.42 ml of water, 2.42 ml of aqueous 15% sodium hydroxide and 7.25 ml of water. After stirring for 1.0 hr, the white slurry of aluminum salts was filtered and thoroughly washed with ether. The combined ether portions were stirred briefly over sodium sulfate, filtered and concentrated on the rotary evaporator. The residue was taken up in methylene chloride and distilled to azetrope off any water that maybe present. Concentration on the rotary evaporator afforded 2.885 g (69%) of cis-diol 130 as a waxy solid: m.p. 48-52° (lit.[110] 60-61.5°); ir($CHCl_3$) 3630 and 3460 (broad) cm^{-1}; nmr($CDCl_3$)δ 3.58 (m, 4, $-CH_2OH$), 2.10 (m, 4, ring protons), 1.15 (s, 3, $-CH_3$), and 1.10 (s, 3, $-CH_3$).

Dimesylate of cis-1,3-Bis(hydroxymethyl)-2,2-dimethylcyclobutane (131).[110] -- To an ice-cold solution of 1.314 g (9.13 mmol) of cis-diol 130 in 10 ml of methylene chloride and 2 ml of pyridine was added 2.30 g (20.1 mmol) of freshly distilled methanesulfonyl chloride [56-59° (14-15 mm)]. The reaction mixture was allowed to warm to room temperature as fast as the ice melted and stirred for 21 hr. The reaction mixture was taken up in ether and washed once with cold aqueous 5% hydrochloric acid, twice with water, and dried over sodium sulfate. Concentration on the rotary evaporator afforded 2.556 g (92%) of dimesylate 131 as a white solid: m.p. 74.5-75.5° (lit.[110] 75-76°); ir($CHCl_3$) 3020, 2960, 1370, 1350, 1180, 980, and 955 cm^{-1}; nmr($CDCl_3$)δ 4.20 (d, 4, J = 7 Hz, $-CH_2OMs$),

3.00 (s, 6, -OMs), 2.65-1.90 (m, 4, ring protons), 1.20 (s, 3, $-CH_3$), and 1.08 (s, 3, $-CH_3$).

6,6-Dimethyl-3-thiabicyclo[3.1.1]heptane (132). -- Using the procedure described for preparing sulfide 121[86] 9.88 g (32.93 mmol) of dimesylate 131 was allowed to react with 24.00 g (100.0 mmol) of sodium sulfide nonahydrate for 26 hr. The reaction mixture was cooled, diluted with 750 ml of brine and extracted with pentane. The combined pentane extracts were washed three times with 50 ml portions of water and dried over sodium sulfate. The pentane was distilled off using a 16" vigreaux column and the residue was briefly put under a vacuum to remove the last traces of pentane. Sulfide 132 was obtained as a yellow liquid (4.32 g, 94.5%): ir(CCl_4) 2960, 1395 and 1375 cm^{-1}; nmr(CCl_4)δ 1.17 (s, 3, $-CH_3$) and 1.10 (s, 3, $-CH_3$).

Anal. Calcd for $C_8H_{14}S$: mol. wt 142.08162. Found(ms): 142.08273.

2-Chloro-6,6-dimethyl-3-thiabicyclo[3.1.1]heptane 3,3-Dioxide (125). -- Using the procedure described for preparing 122[86] 1.15 g (8.08 mmol) of sulfide 132 was allowed to react with 1.09 g (8.20 mmol) of N-chlorosuccinimide in 25 ml of carbon tetrachloride for 5.5 hr. The reaction mixture was filtered and the solid was washed with carbon tetrachloride. Concentration on the rotary evaporator afforded a brown residue that was dissolved in 20 ml of dry ether and cooled to 0° with an ice-bath. To this cooled solution a solution of 3.296 g of 85% m-chloroperbenzoic acid in 25 ml of dry ether was added over a period of 30 min. The reaction mixture was allowed to warm at a rate at which the ice melted and stirred for 20.5 hr at which time it was poured into a separatory funnel and washed twice with 25 ml portions of aqueous 1 N sodium hydroxide, twice with 25 ml portions of water, once with 20 ml of brine,

and dried over sodium sulfate. Concentration on the rotary evaporator afforded 1.04 g (50%) of crude 125 as a yellow viscous liquid. The nmr spectrum indicated that the mixture consisted of 75% of 125 and 25% of starting material dioxide. An analytical sample of 125 was obtained as a clear liquid by preparative thin layer chromatography:[114] ir($CHCl_3$) 1330 and 1130 cm^{-1}; nmr($CDCl_3$)δ 5.28 (m, 2, -CHCl-), 3.74 (d, 2, J = 3 Hz, $-CH_2SO_2-$), 2.6-1.9 (m, 4, ring protons), 1.44 (s, 3, $-CH_3$), and 1.30 (s, 3, $-CH_3$).

Anal. Calcd for $C_8H_{13}SO_2Cl$: C, 46.03; H, 6.27. Found: C, 46.21; H, 6.26.

5,5-Dimethylbicyclo[2.1.1]hex-2-ene (126). -- Using the procedure described for preparing olefin 78[87] 117 mg of purified chlorosulfone 125 was allowed to react with 2.0 mmol of tert-amyl alcoholate in 12 ml of diphenyl ether. From this was obtained 24 mg (40%) of olefin 126 that was shown by vpc[103] analysis to be contaminated with 3% tert-amyl alcohol. The olefin was purified by preparative vpc[115] to give an analytical sample: ir(CCl_4) 3110, 3070, 3040, 1380, 1365, 705 and 610 cm^{-1}; nmr(CCl_4)δ 6.63 (t, 2, J = 2 Hz, olefin protons), 3.00 (m, 1, C-6 anti-[112] proton), 2.27 (dd, 2, J = 2.0 and 6.0 Hz, bridgehead protons), 2.02 (d, 1, J = 6 Hz, C-6 syn-[112] proton), 1.52 (s, 3, anti-CH_3), and 1.03 (s, 3, syn-CH_3).

Anal. Calcd for C_8H_{12}: mol. wt. 108.09384. Found: 108.09400.

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91. A 6' x ¼" column packed with 15% PPGA on 60/80 Chrom W support was used in this analysis.

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97. A 10' x ¼" column packed with 10% C20M, 10% NaOH on 60/80 Chrom W support was used in this analysis.

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99. A 6' x ¼" column packed with 15% C20M on 60/80 Chrom W support was used in this analysis.

100. The reaction was allowed to continue until consumption of starting material had ceased as determined by vpc monitoring.[91]

101. This yield could be somewhat low due to the volatile nature of the epoxide.

102. By monitoring the reaction on vpc,[91] all the starting material had been consumed after 7 hr.

103. A 6' x ¼" column packed with 15% Dow-710 on 60/80 Chrom W support was used in this analysis.

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105. A 6' x ¼" column packed with 15% SF-96 on 60/80 Chrom W support was used in this analysis.

106. The workers in reference #83 reported a melting point of 131-132°, while K.D. Stueben[107] reported a melting point of 152-153°.

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111. This crude material was used in the next step without further purification.

112. In this context syn and anti denotes those hydrogens which are on the same side or opposite side, respectively, as the double bond.

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114. A 20 x 20 cm Silplate-F-22 preparative tlc plate was used eluting with benzene/ethyl acetate (78:2). A double elution procedure was used.

115. A 10' x $\frac{3}{8}$" column packed with 10% Dow-710 on 60/80 Chrom W support was used.

NUCLEAR MAGNETIC RESONANCE SPECTRA

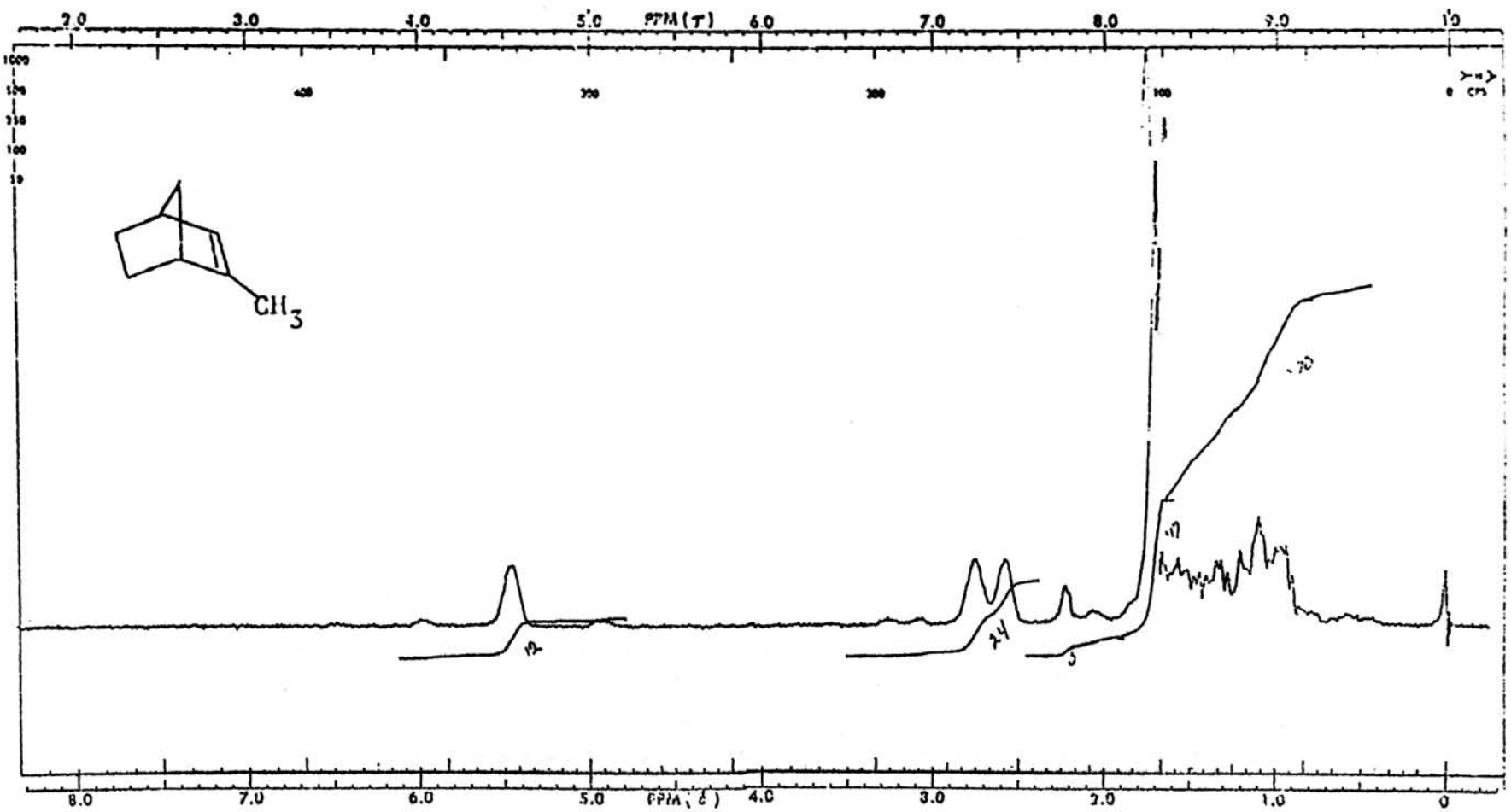

Fig. 1. 60 MHz NMR Spectrum of 2-Methylnorbornene (81) in CCl_4. (500 Hz Sweep Width).

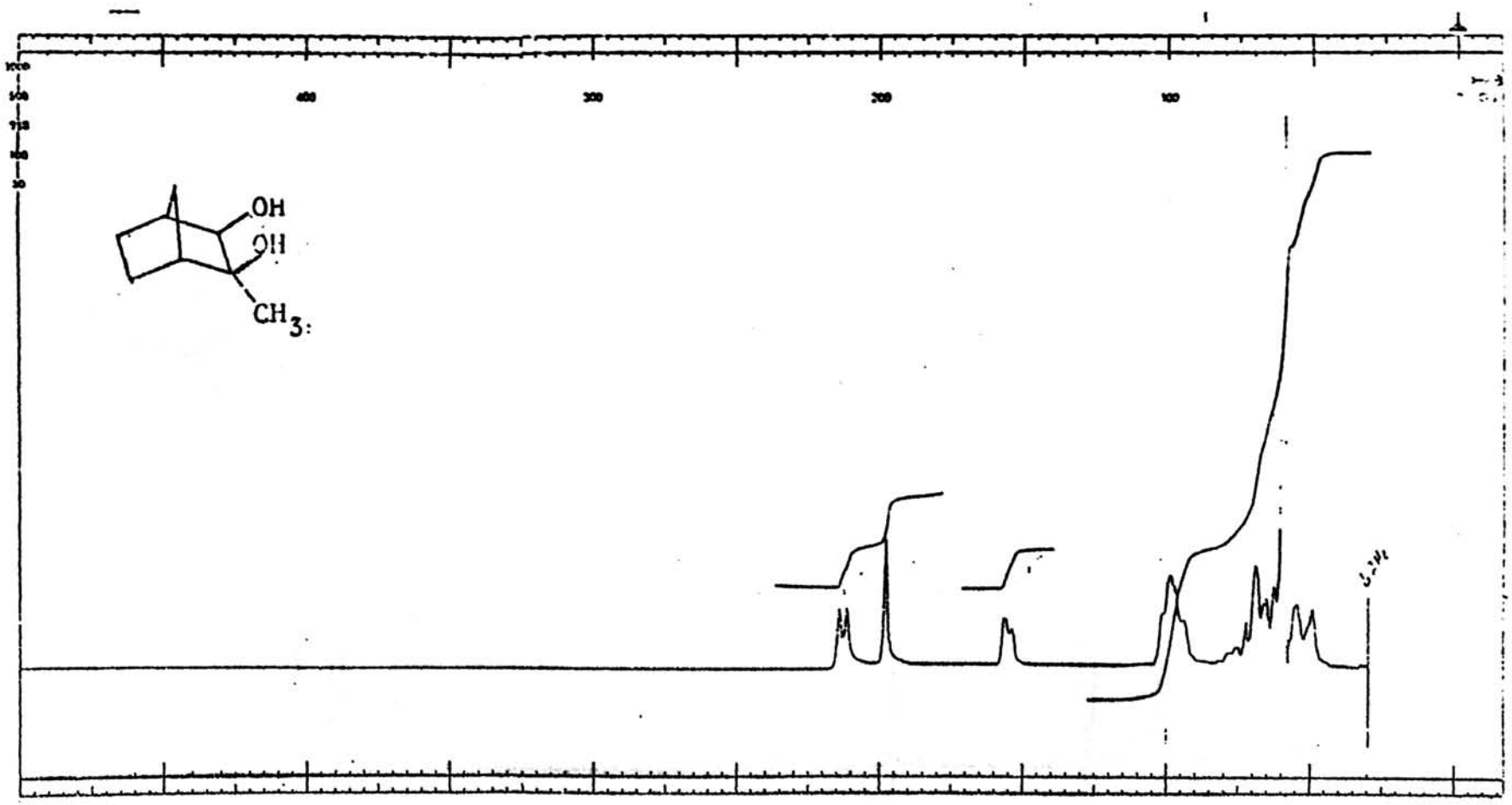

Fig. 2. 100 MHz NMR Spectrum of 2-endo-Methyl-2,3-cis,exo-norbornanediol (80) in CCl_4. (1000 Hz Sweep Width).

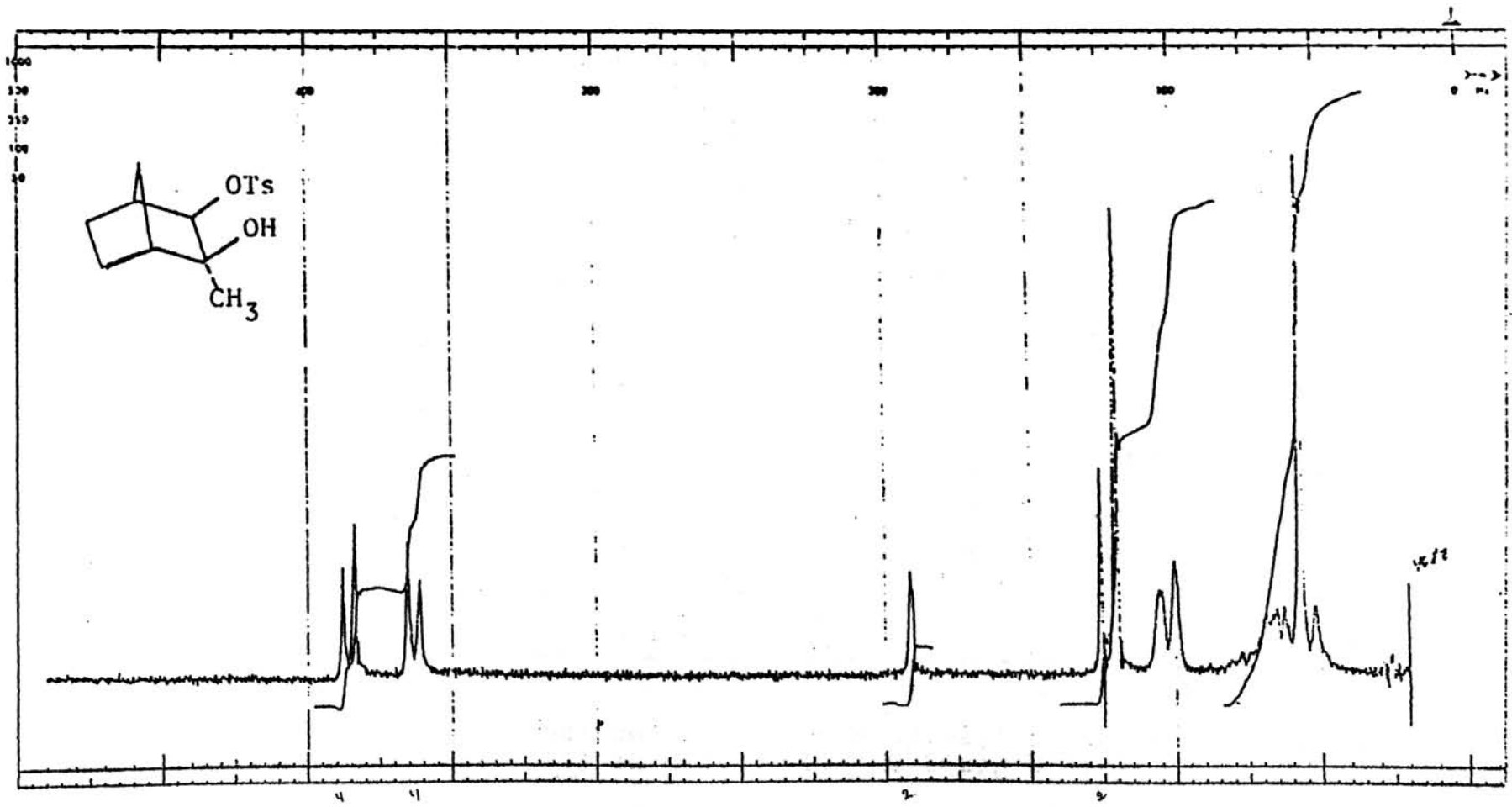

Fig. 3. 100 MHz NMR Spectrum of 2-endo-Methyl-2,3-cis,exo-norbornanediol 3-p-Toluenesulfonate (20) in CCl_4. (1000 Hz Sweep Width).

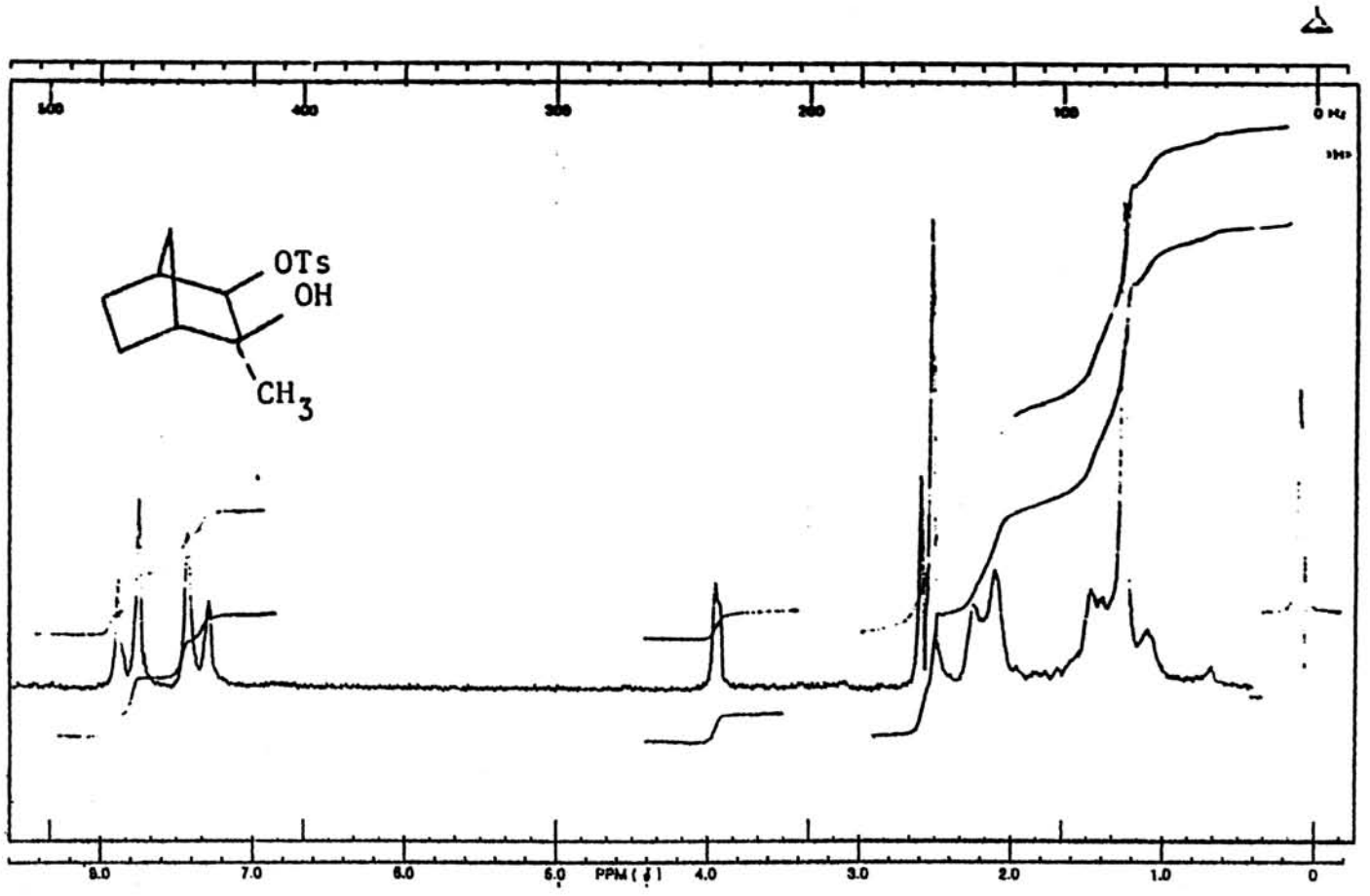

Fig. 4. 60 MHz NMR Spectrum of 2-endo-Methyl-2,3-cis,exo-norbornanediol 3-p-Toluenesulfonate (20) in CCl_4. (500 Hz Sweep Width).

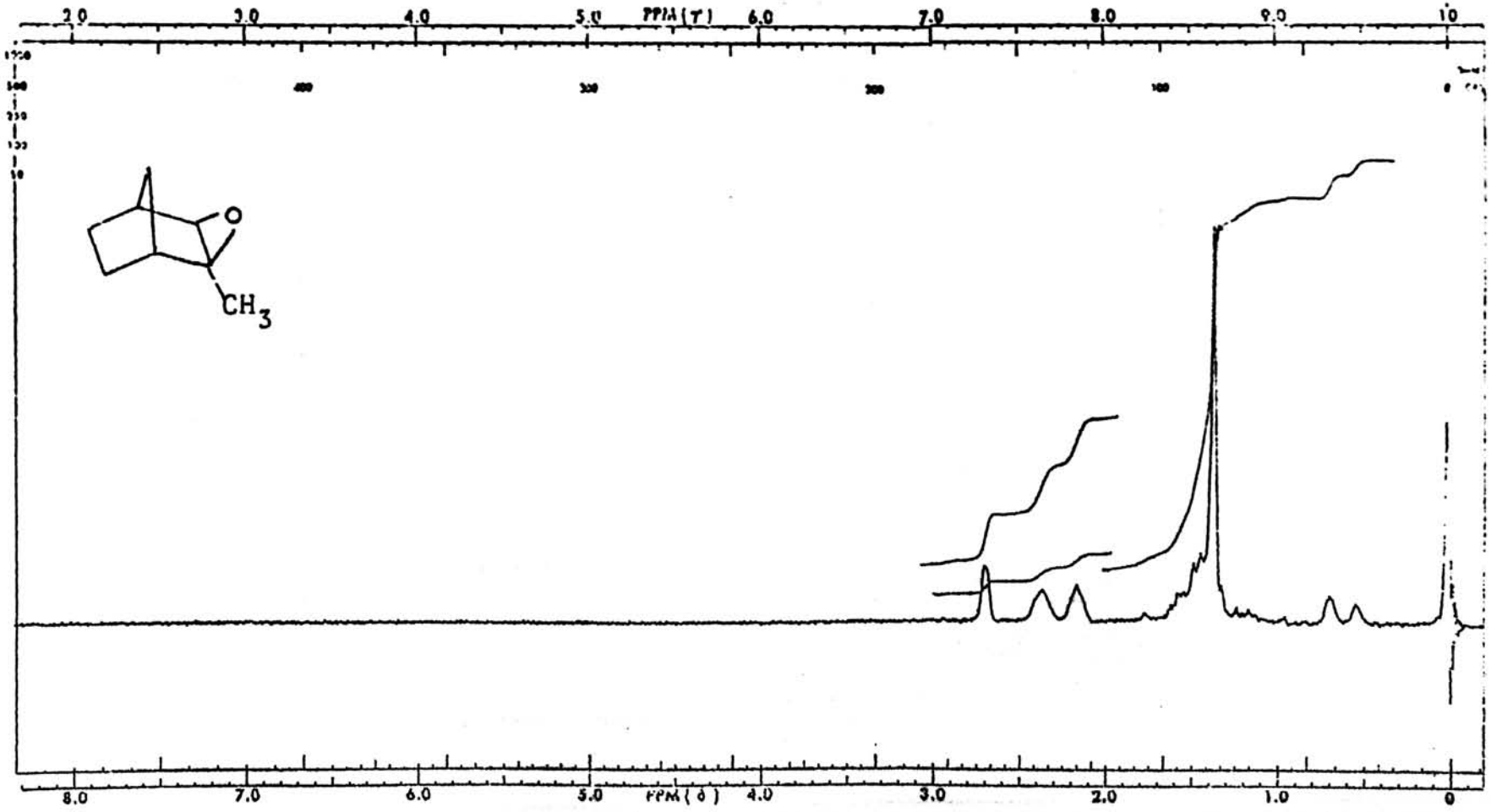

Fig. 5. 60 MHz NMR Spectrum of 2-endo-Methyl-2,3-exo-epoxynorbornane (87) in CCl_4. (500 Hz Sweep Width).

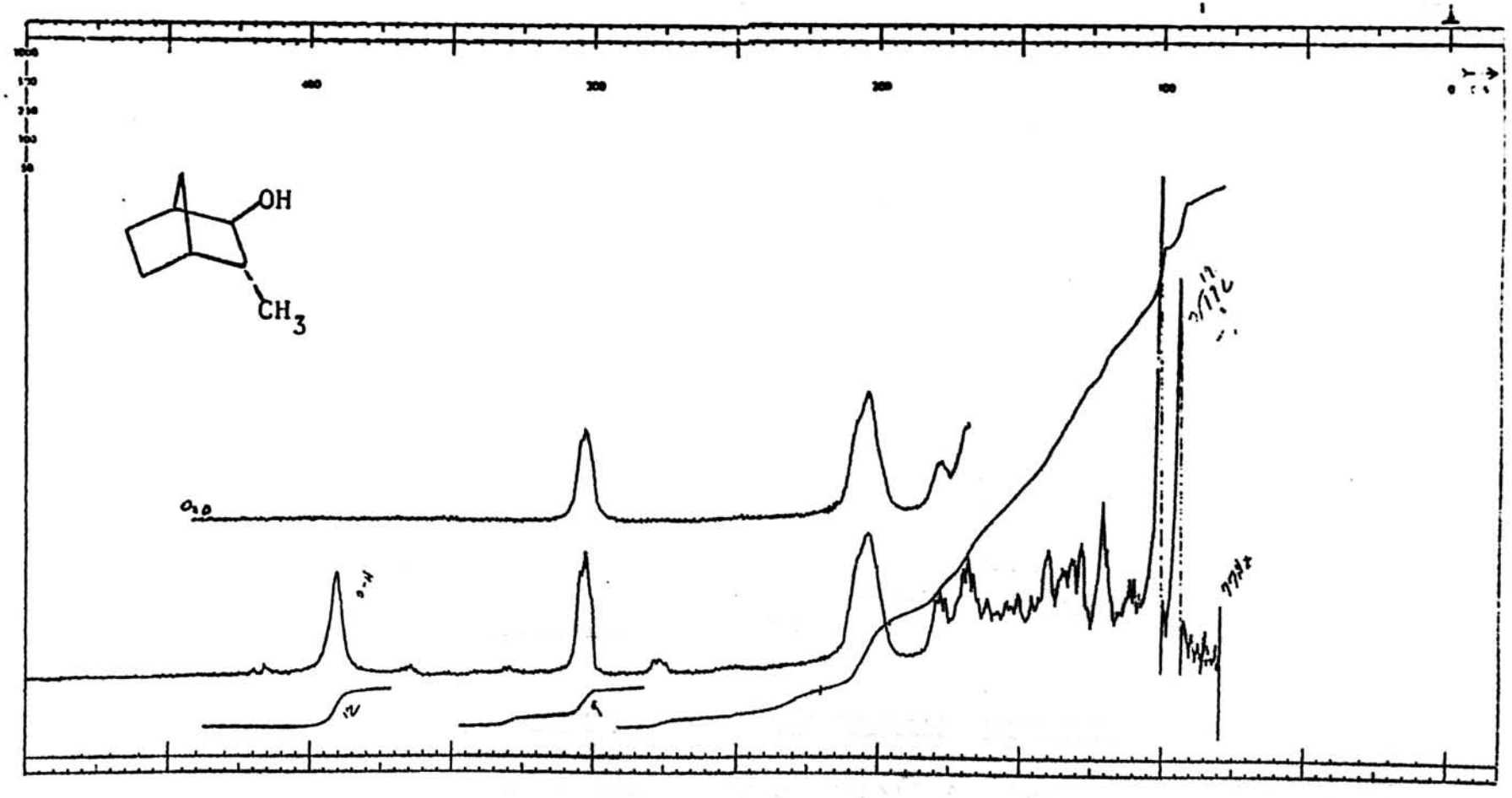

Fig. 6. 100 MHz NMR Spectrum of 3-endo-Methyl-2-exo-norbornanol (93) in CCl_4. (500 Hz Sweep Width).

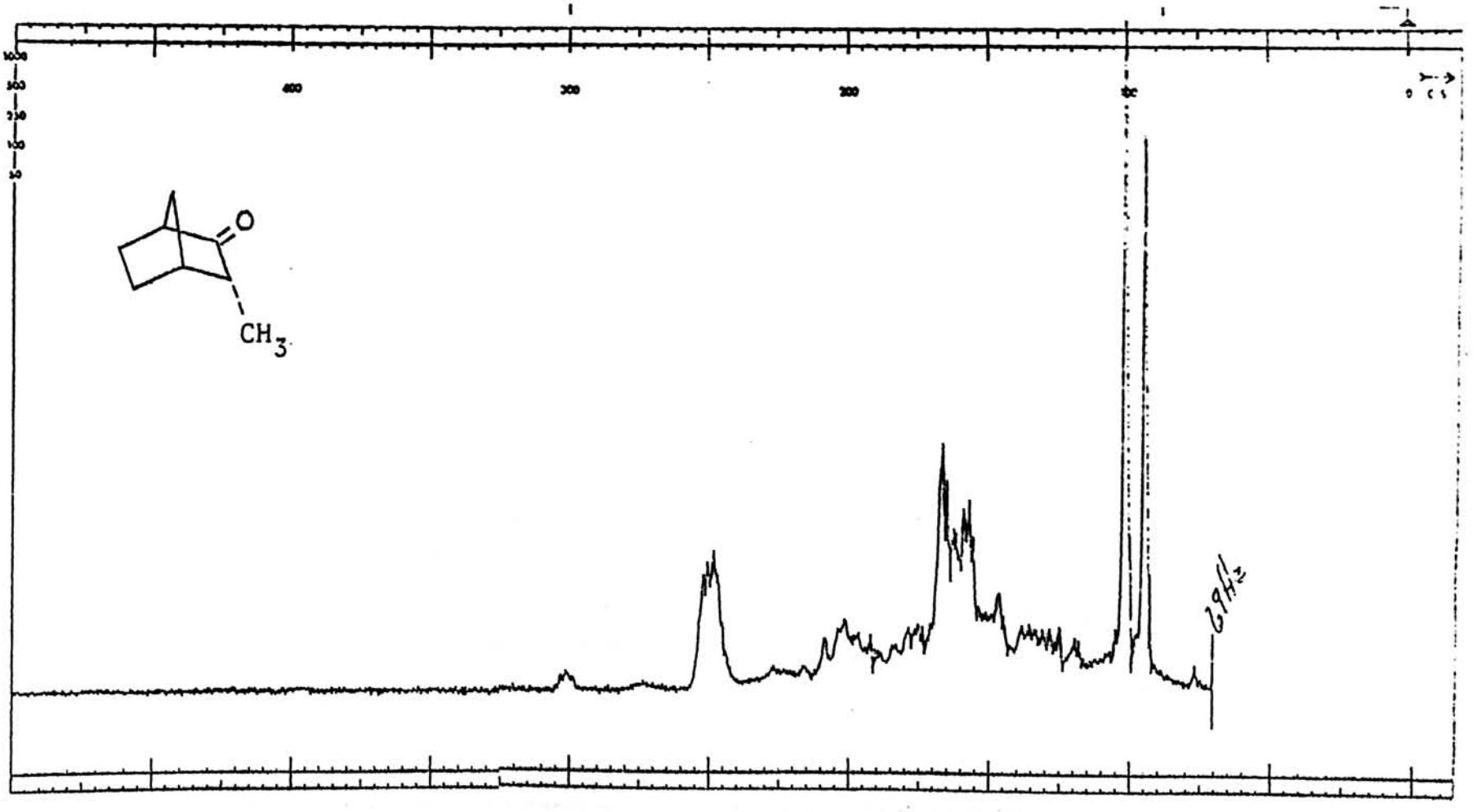

Fig. 7. 100 MHz NMR Spectrum of 3-endo-Methylbicyclo[2.2.1]heptan-2-one (94) in CCl_4). (500 Hz Sweep Width).

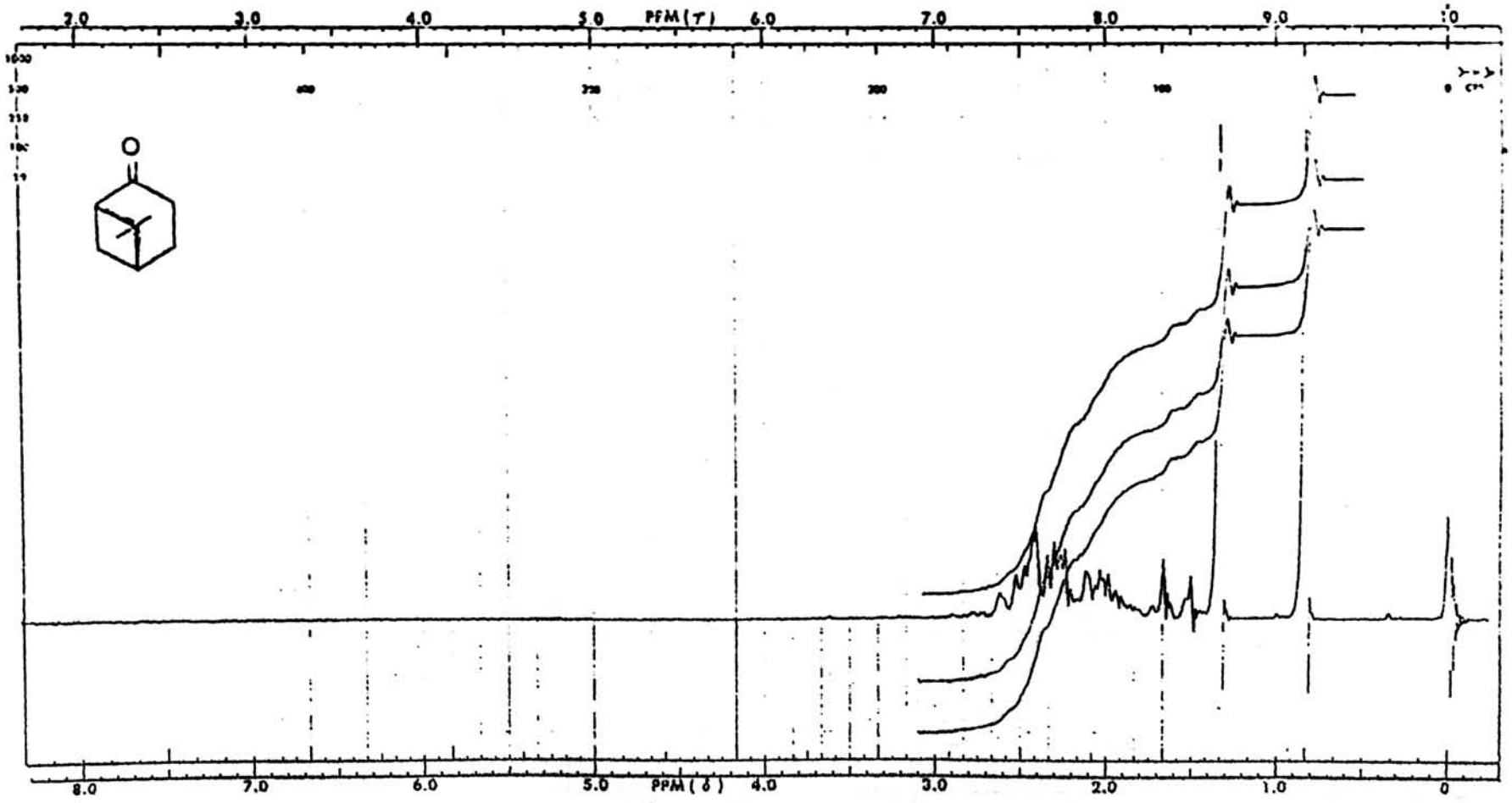

Fig. 8. 60 MHz NMR Spectrum of Nopinone (108) in CCl_4. (500 Hz Sweep Width).

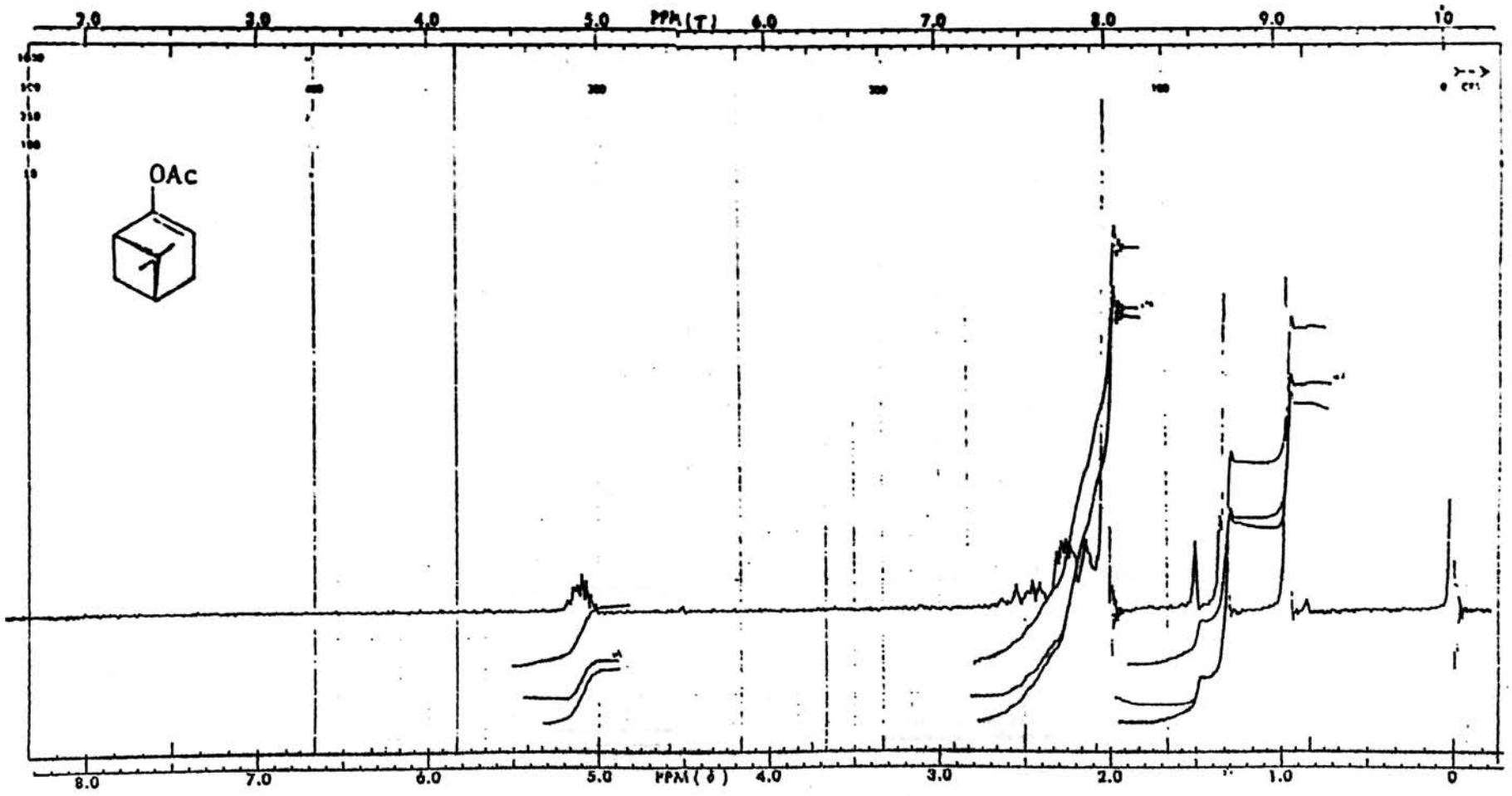

Fig. 9. 60 MHz NMR Spectrum of 2-Acetoxypin-2-ene (109) in CCl_4. (500 Hz Sweep Width).

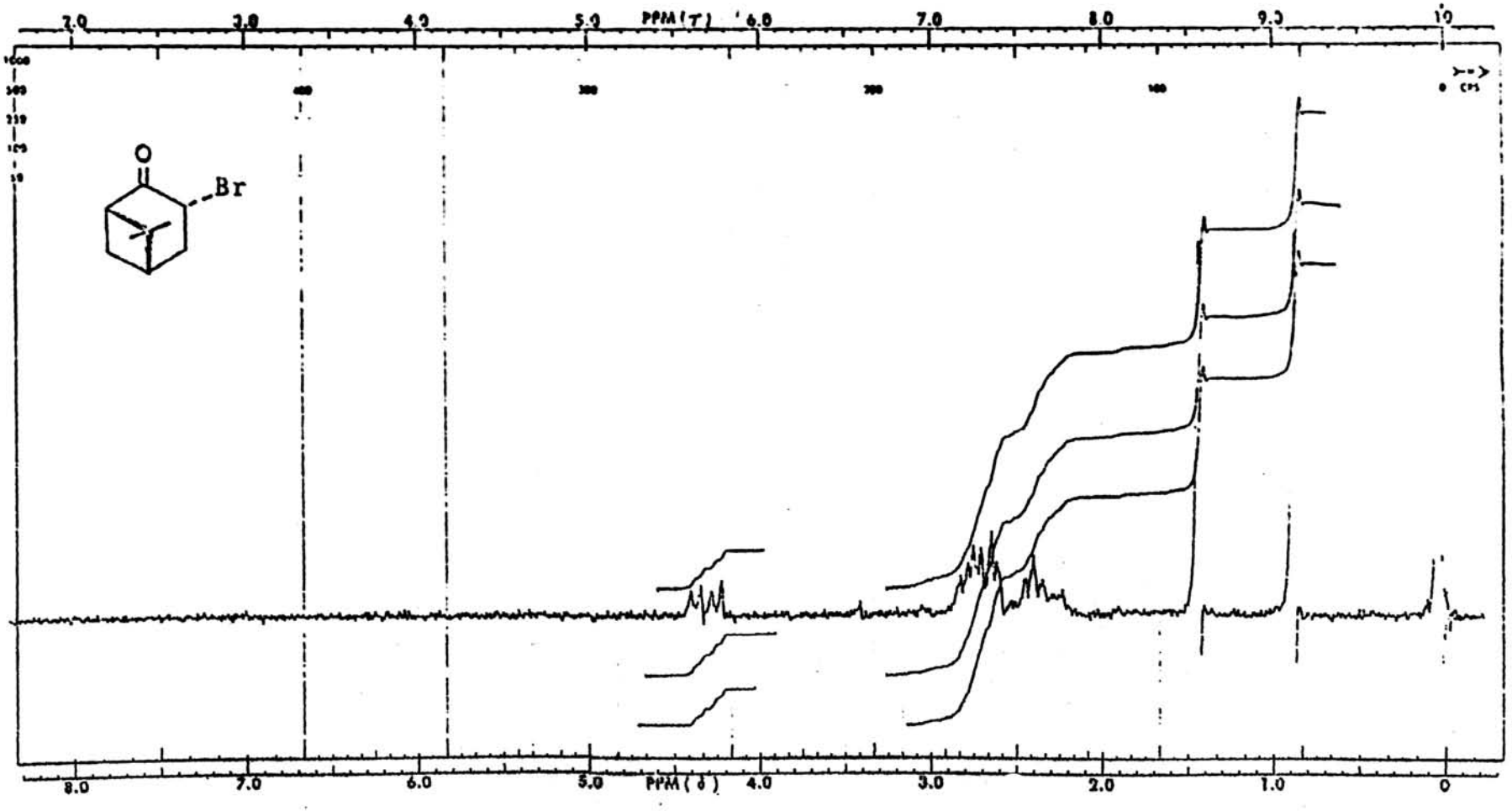

Fig. 10. 60 MHz NMR Spectrum of 3-α-Bromonopinone (110a) in CCl_4. (500 Hz Sweep Width).

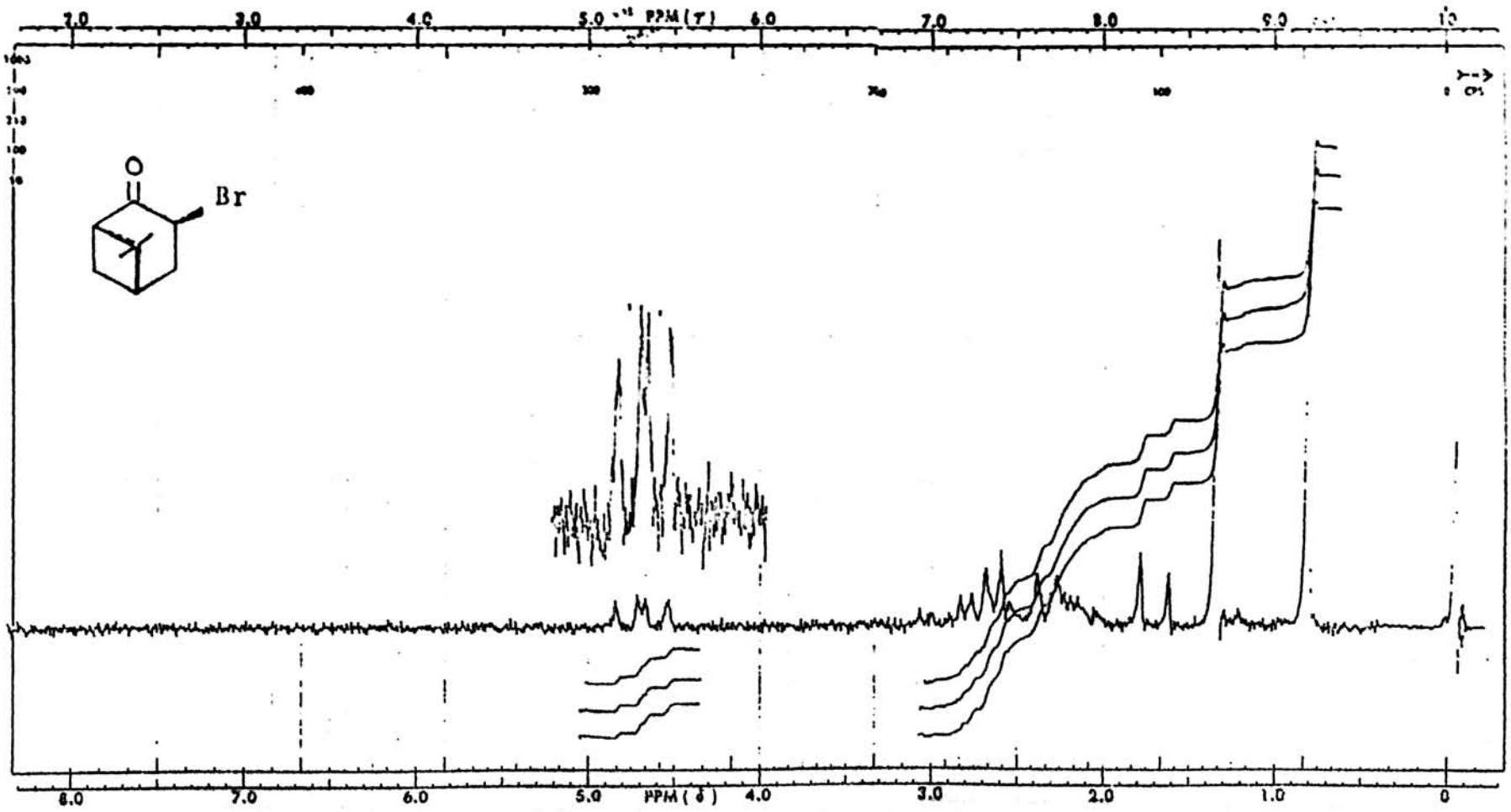

Fig. 11. 60 MHz NMR Spectrum of 3-β-Bromonopinone (110b) in CCl_4. (500 Hz Sweep Width).

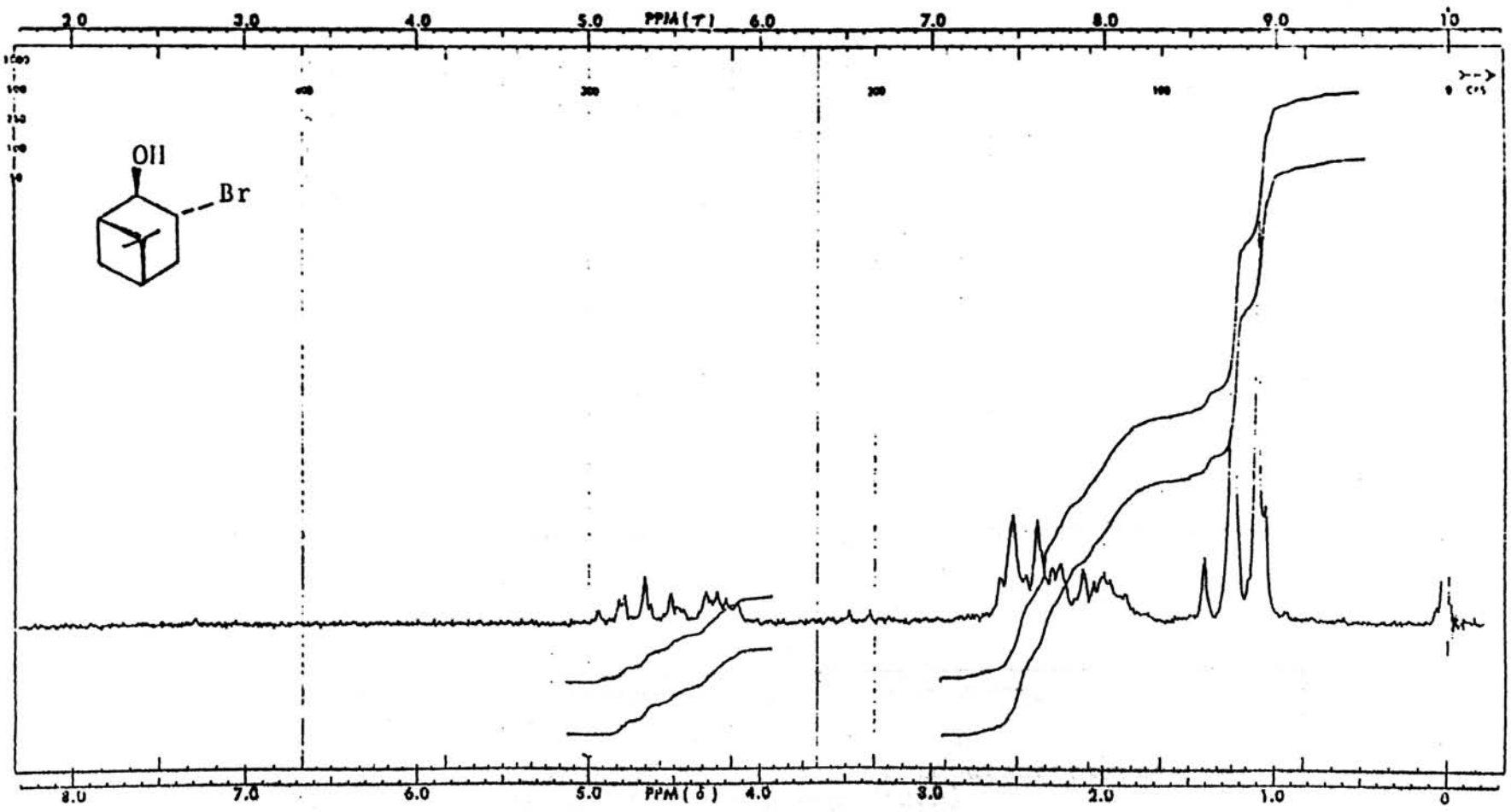

Fig. 12. 60 MHz NMR Spectrum of 2-$\underline{\beta}$-Hydroxy-3-$\underline{\alpha}$-bromopinane (35) in CCl_4. (500 Hz Sweep Width).

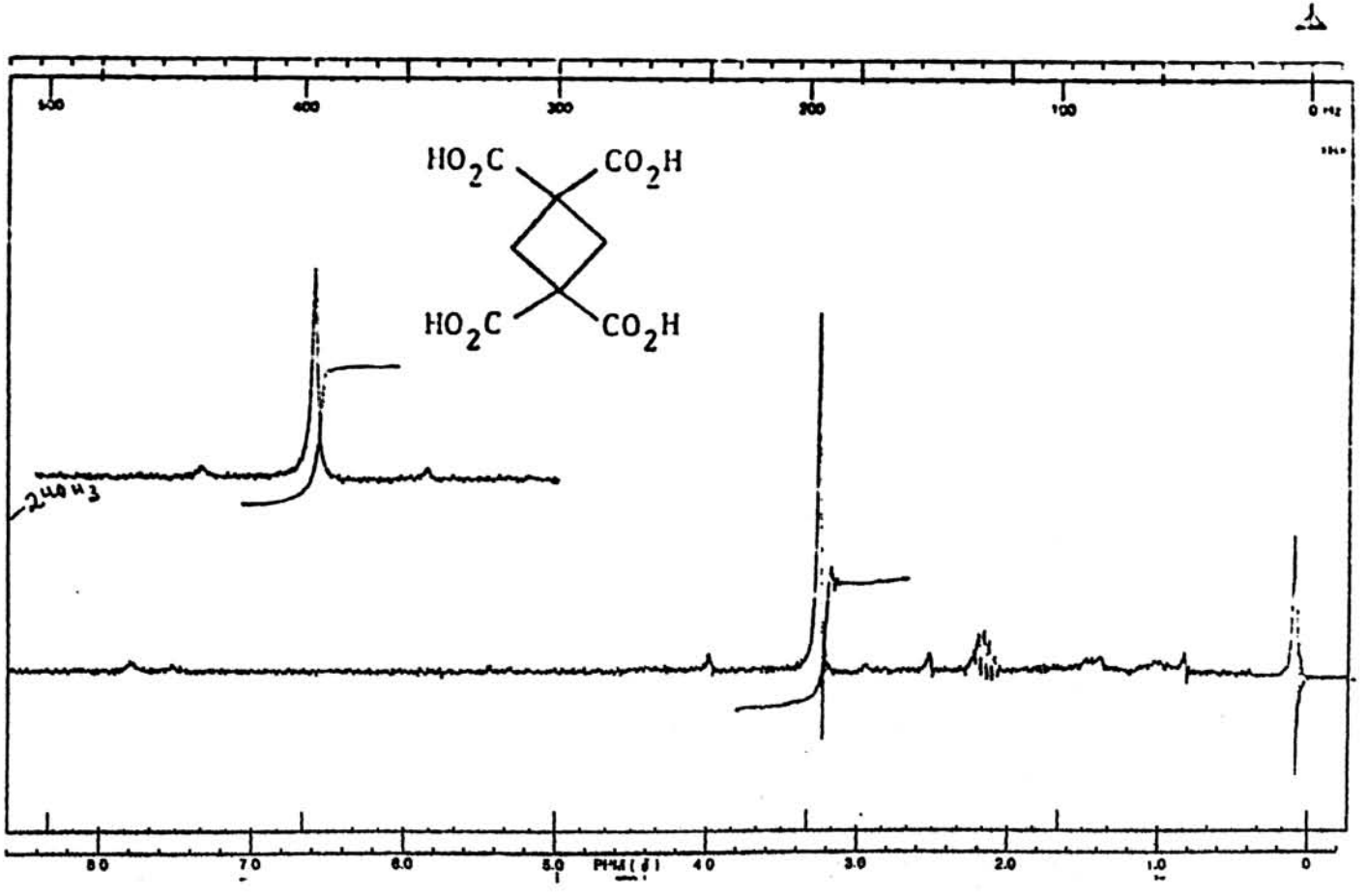

Fig. 13. 60 MHz NMR Spectrum of 1,1,3,3-Cyclobutanetetracarboxylic Acid (116) in Acetone-d_6. (500 Hz Sweep Width).

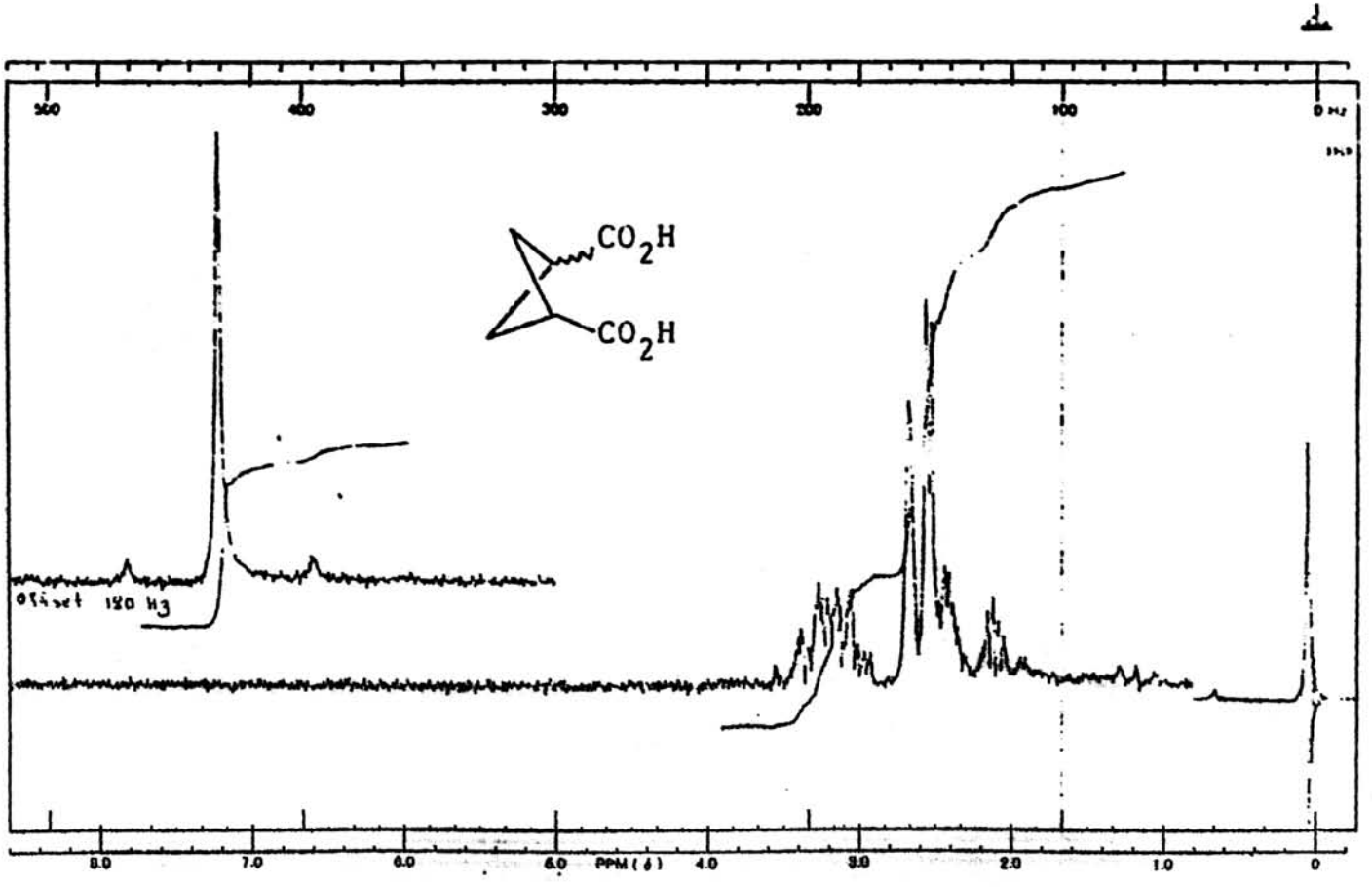

Fig. 14. 60 MHz NMR Spectrum of cis- and trans-1,3-Cyclobutanedicarboxylic Acid (117a and 117b) in Acetone-d_6. (500 Hz Sweep Width).

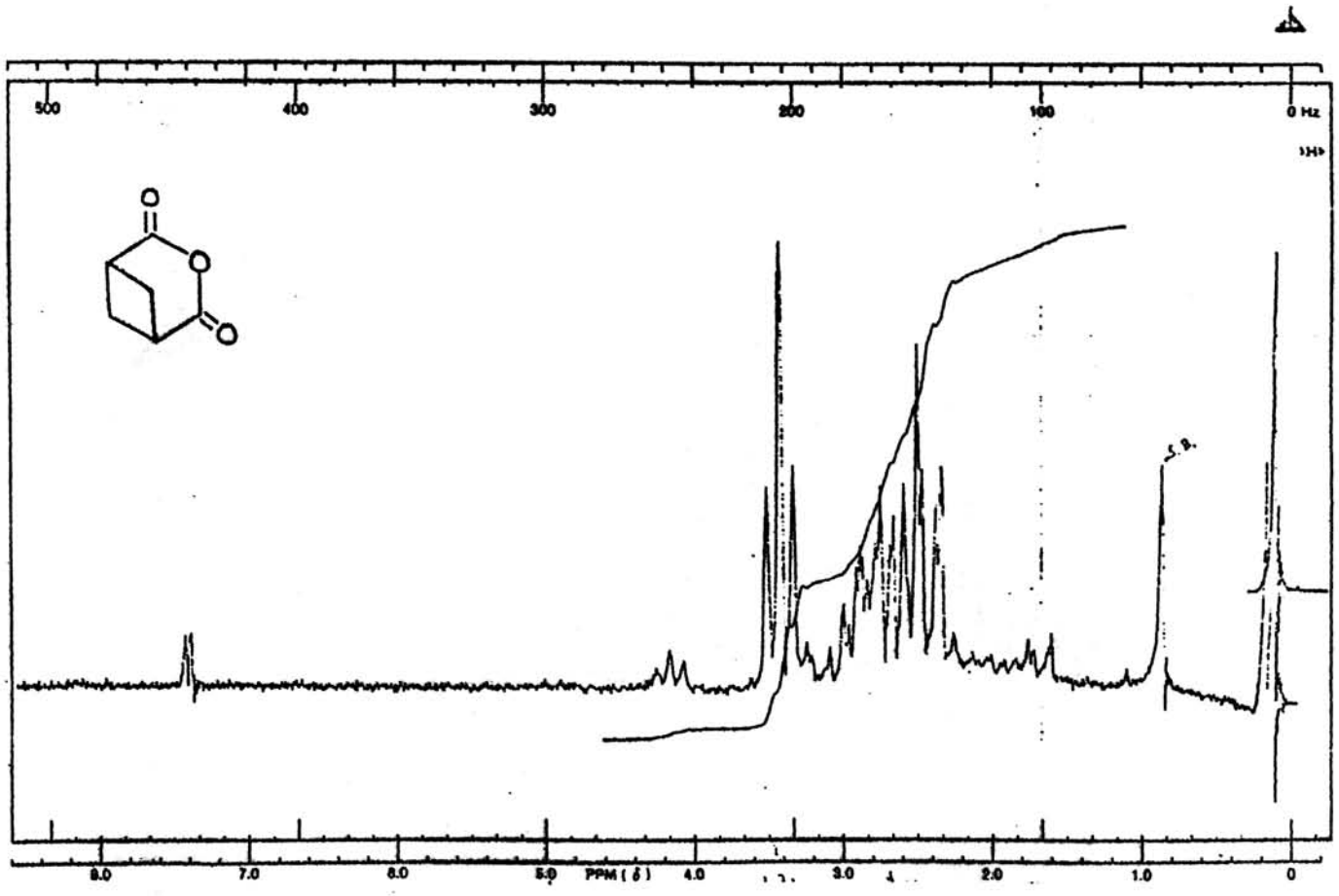

Fig. 15. 60 MHz NMR Spectrum of cis-1,3-Cyclobutanedicarboxylic Acid Anhydride (118) in $CDCl_3$. (500 Hz Sweep Width).

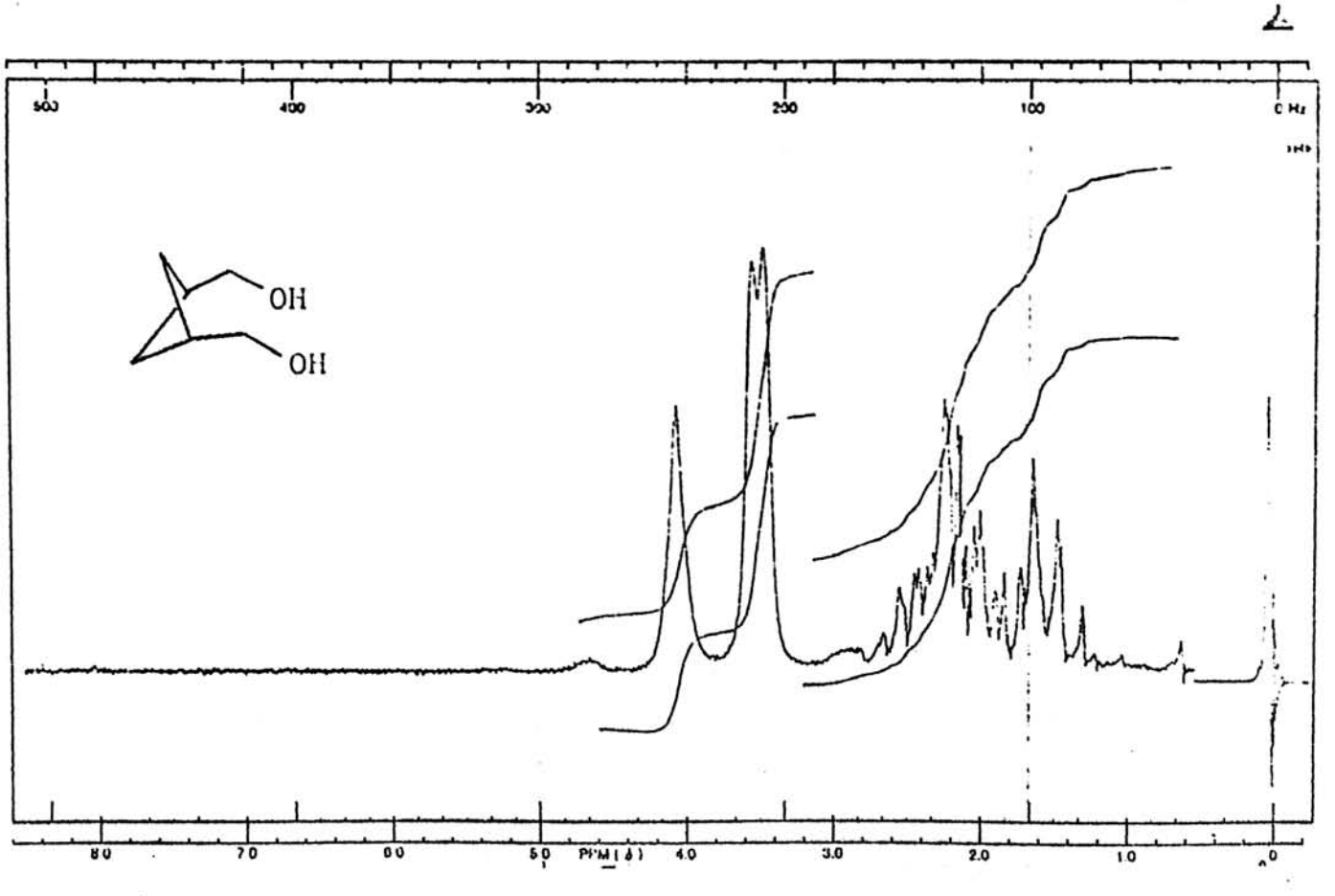

Fig. 16. 60 MHz NMR Spectrum of cis-1,3-Bis(hydroxymethyl)cyclobutane (119) in Acetone-d_6. (500 Hz Sweep Width).

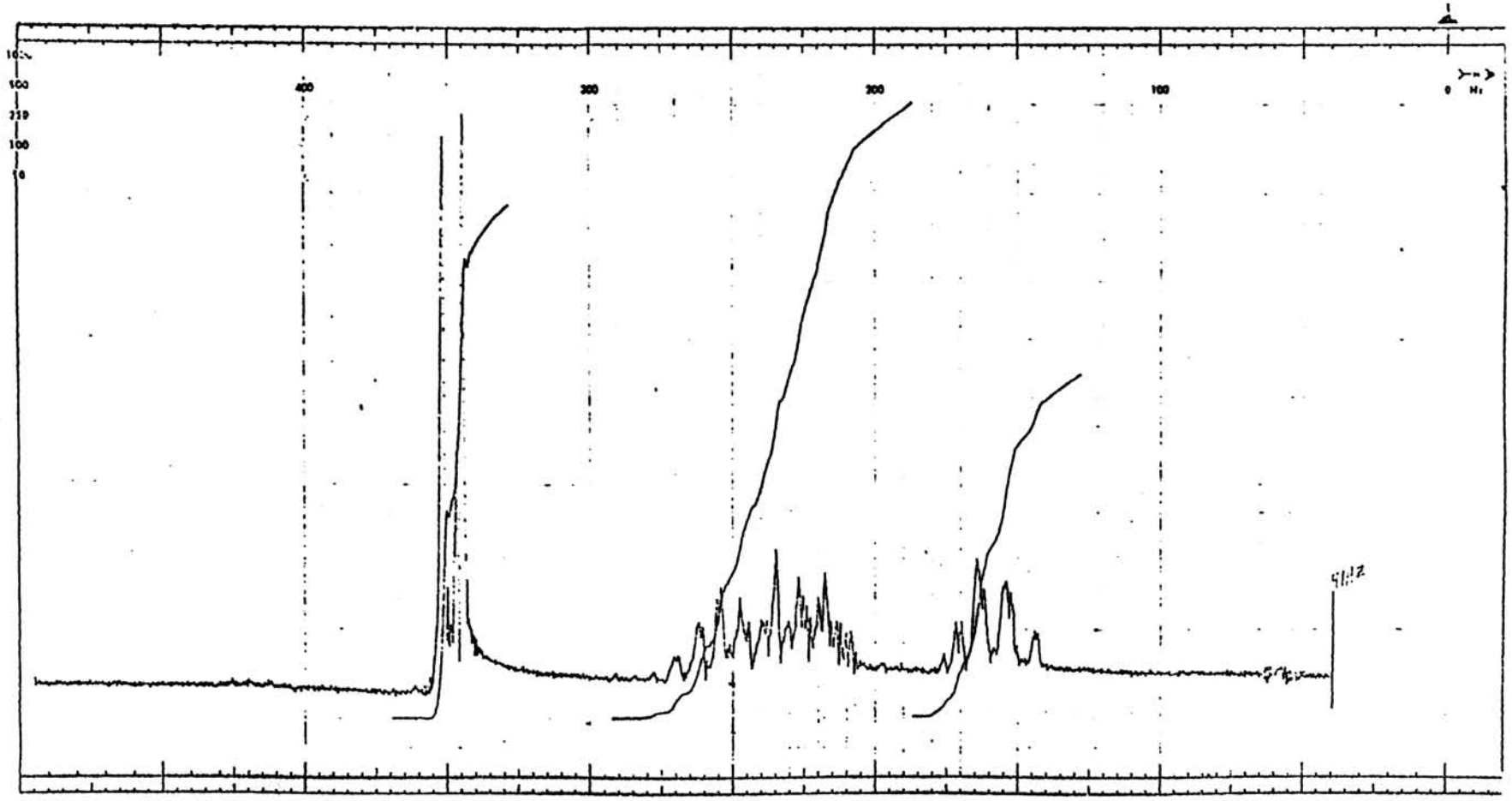

Fig. 17. 100 MHz NMR Spectrum of Component A in $CDCl_3$. (500 Hz Sweep Width).

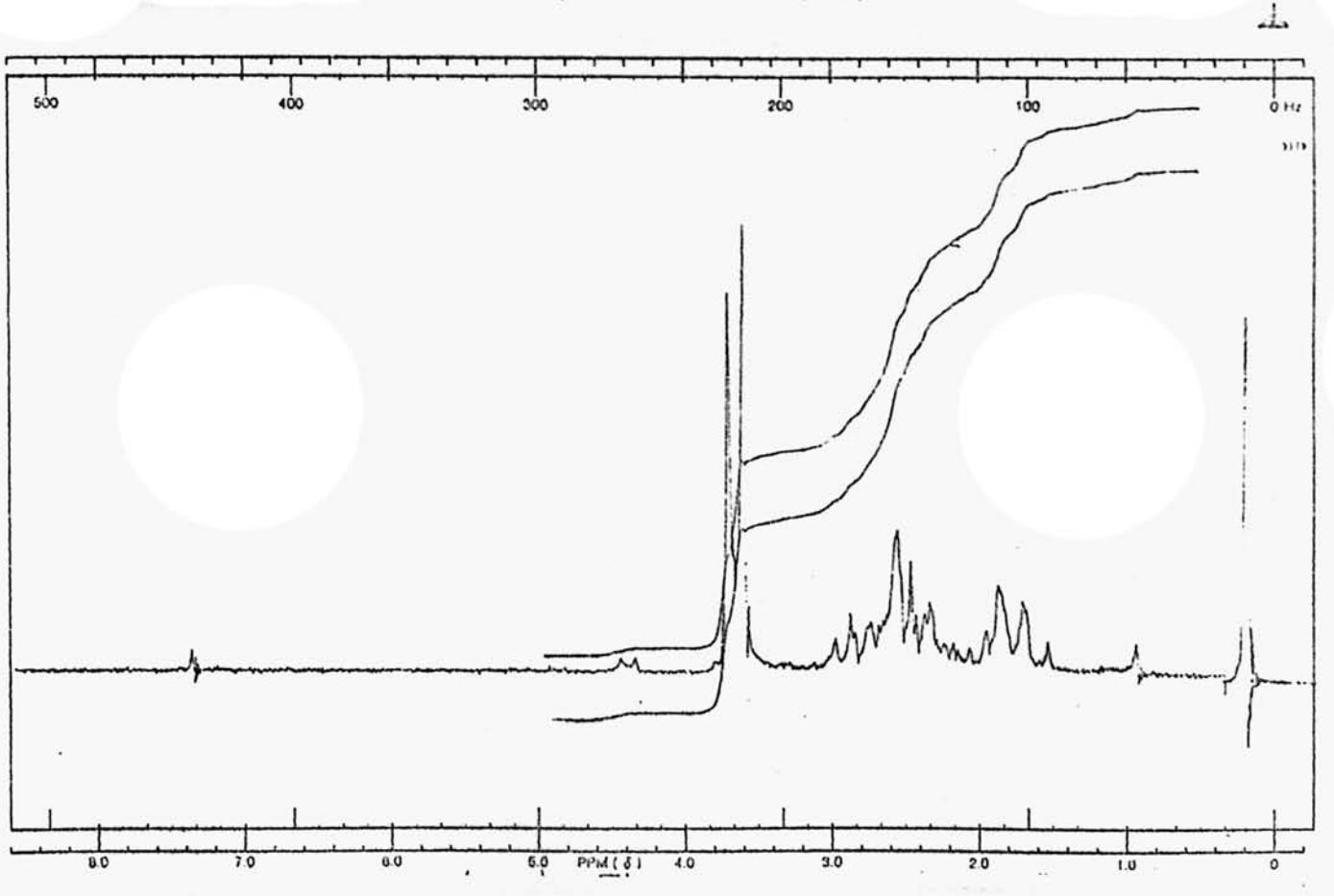

Fig. 18. 60 MHz NMR Spectrum of Component A in $CDCl_3$. (500 Hz Sweep Width).

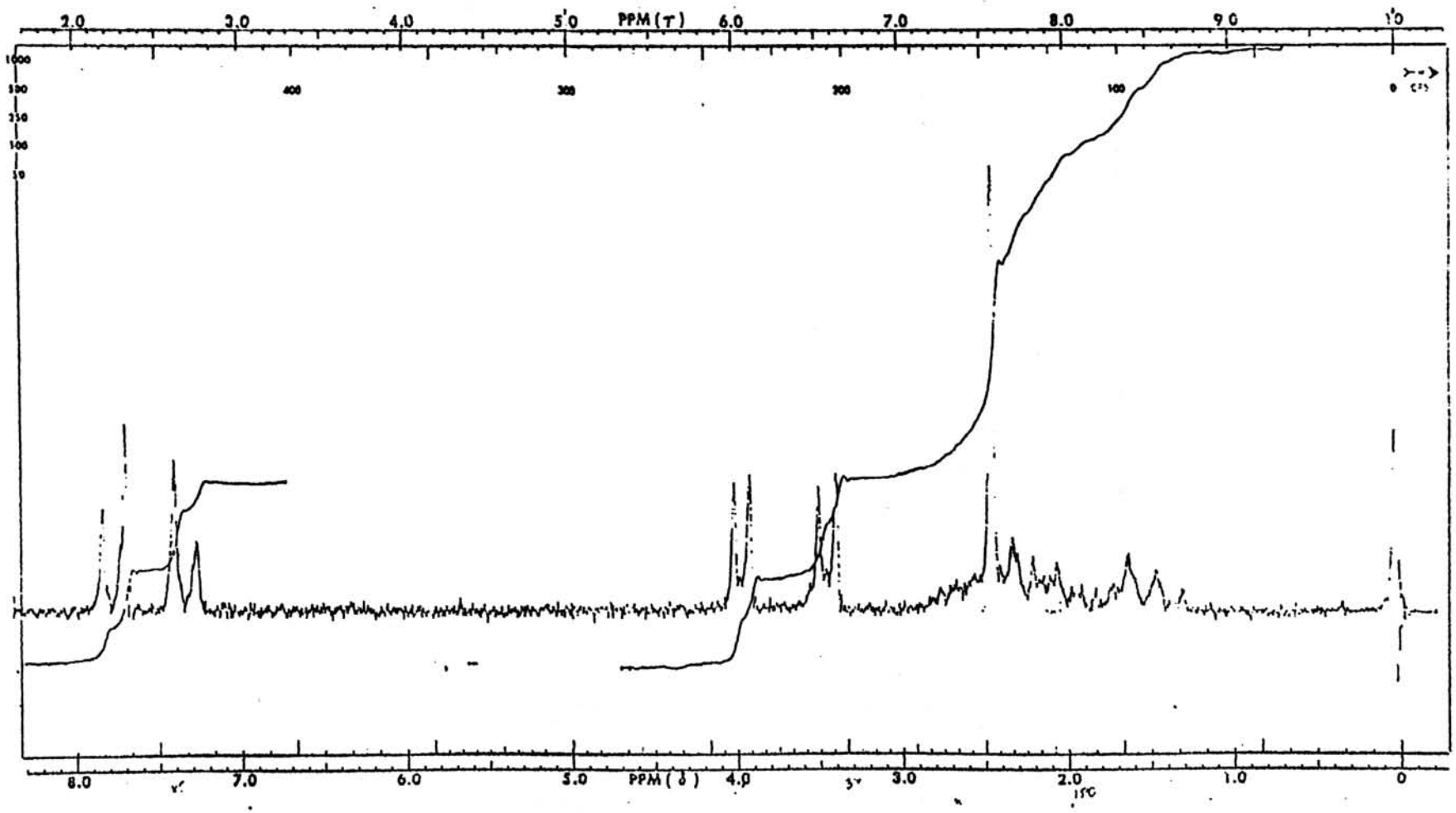

Fig. 19. 60 MHz NMR Spectrum of Component B in $CDCl_3$. (500 Hz Sweep Width).

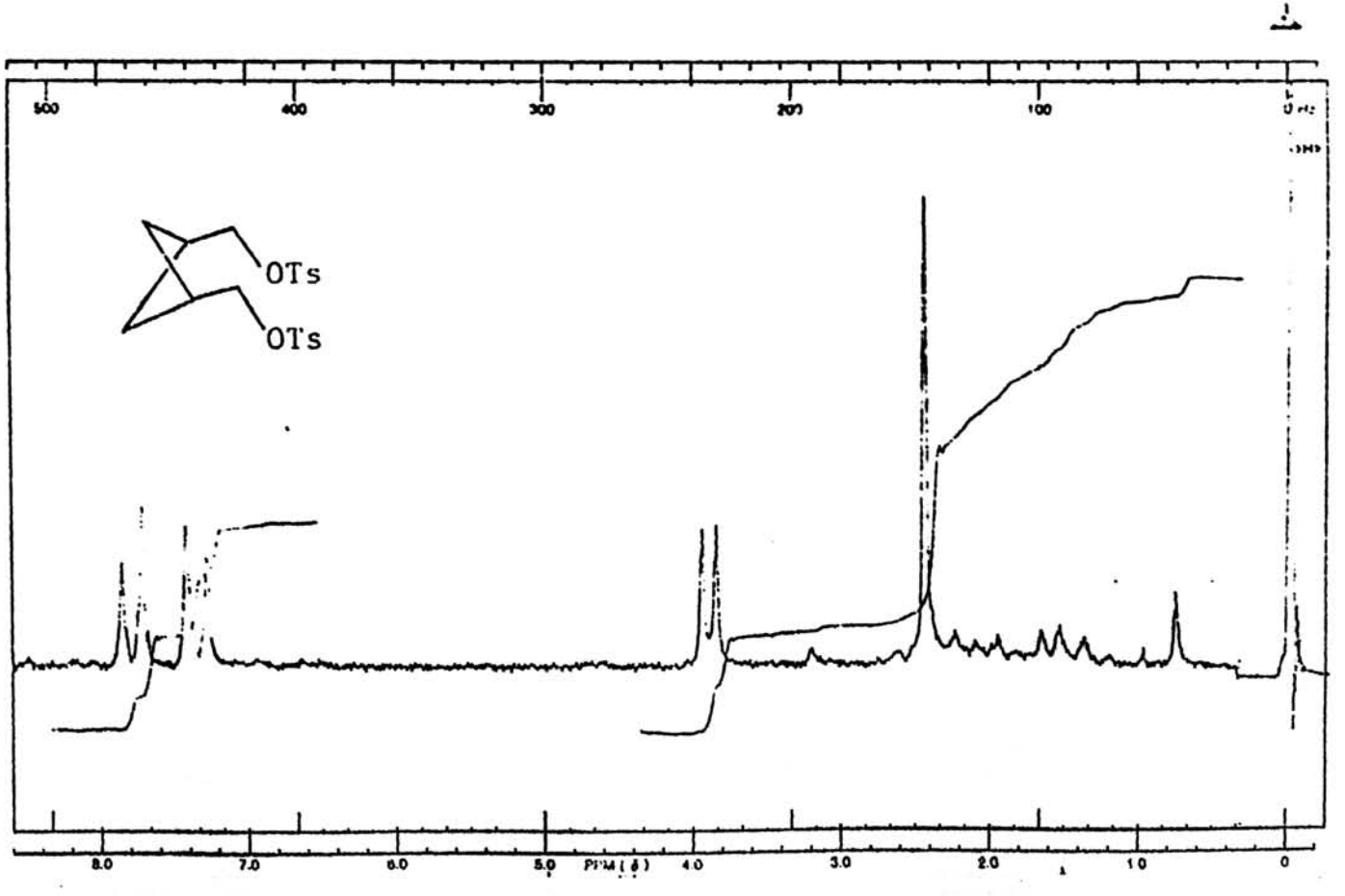

Fig. 20. 60 MHz NMR Spectrum of the Ditosylate of cis-1,3-Bis(hydroxymethyl)cyclobutane (120a) in $CDCl_3$. (500 Hz Sweep Width).

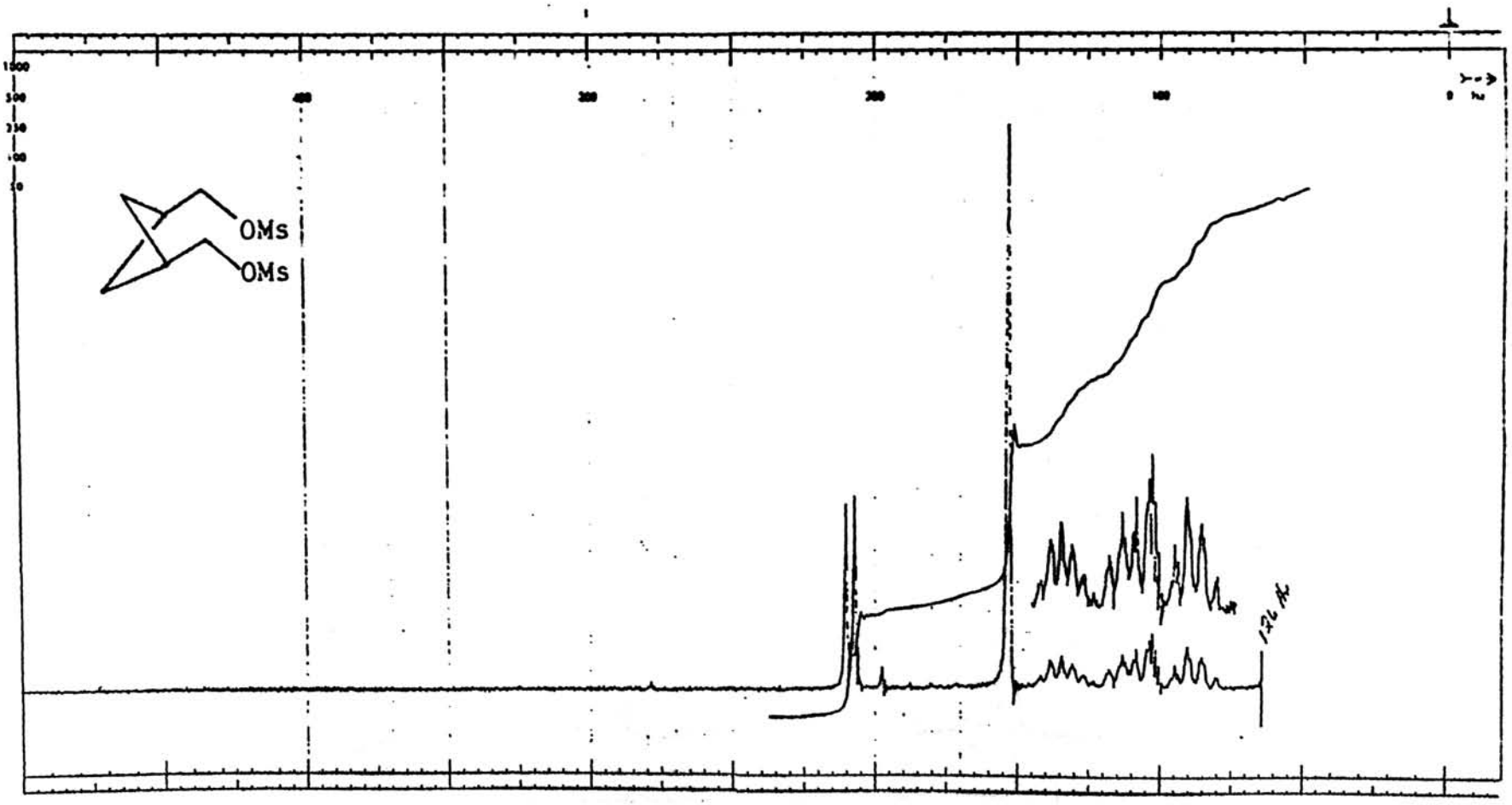

Fig. 21. 100 MHz NMR Spectrum of the Dimesylate of cis-1,3-Bis(hydroxymethyl)cyclobutane (120b) in Acetone-d_6. (1000 Hz Sweep Width).

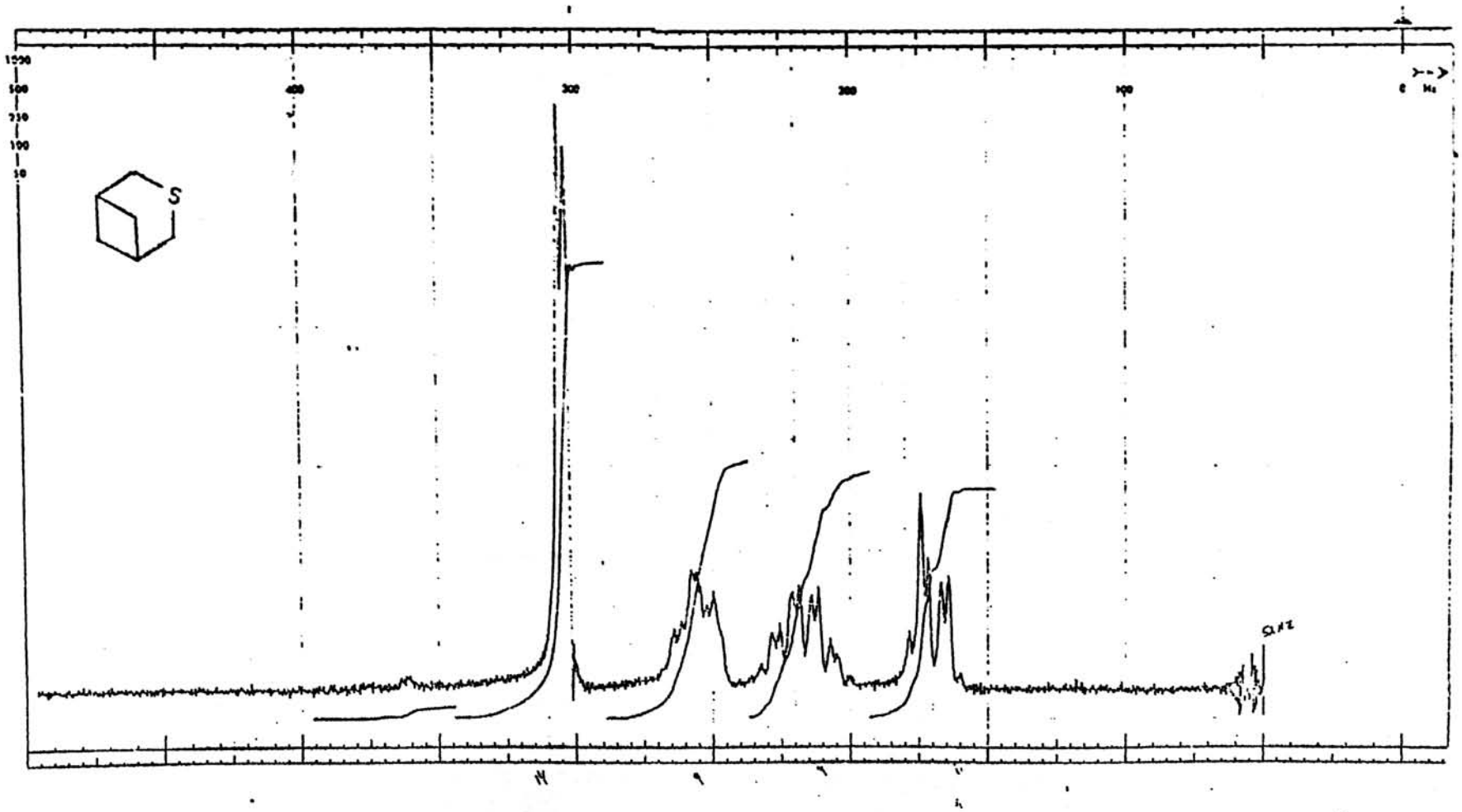

Fig. 22. 100 MHz NMR Spectrum of 3-Thiabicyclo[3.1.1]heptane (121) in CCl_4. (500 Hz Sweep Width).

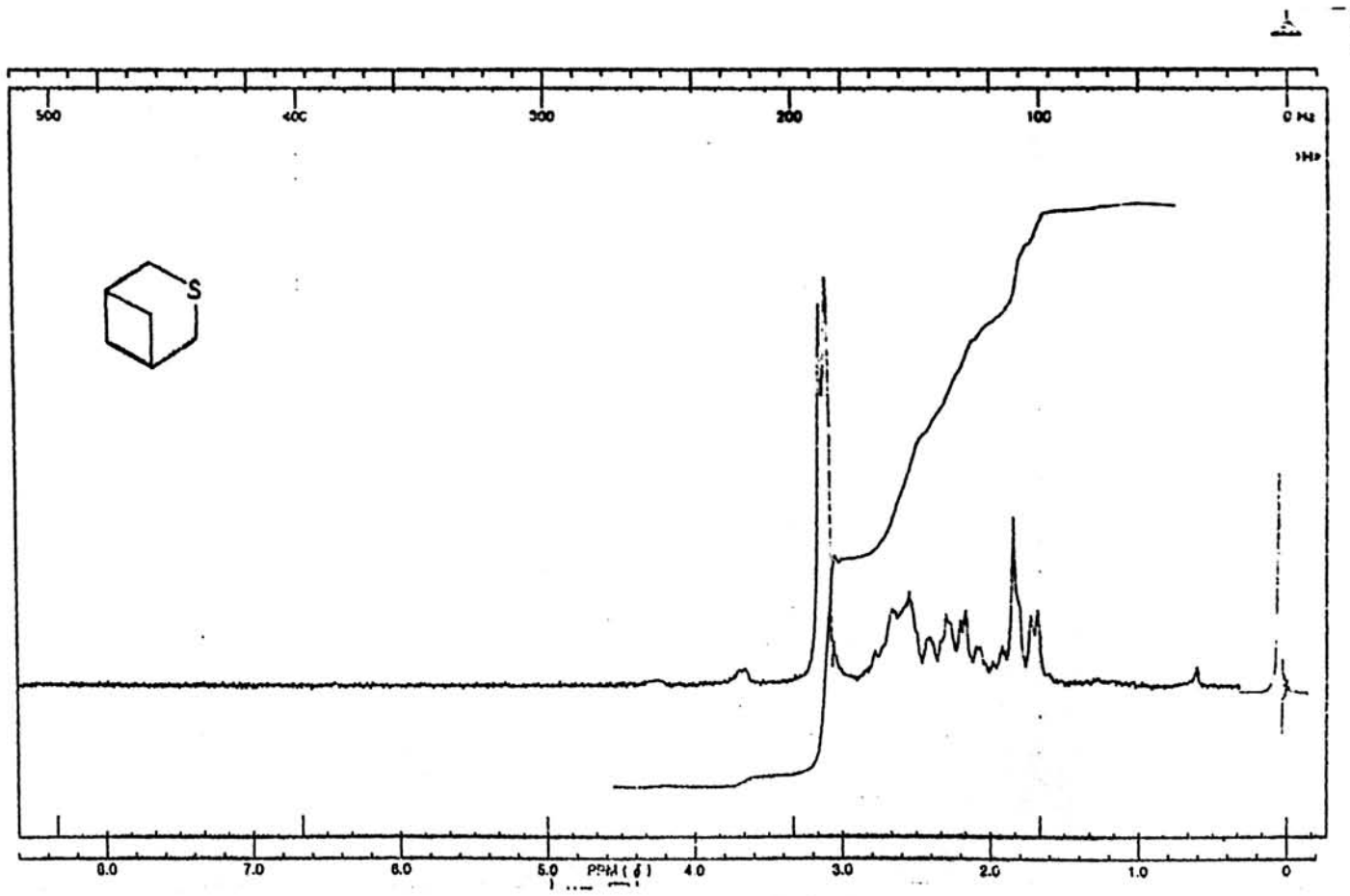

Fig. 23. 60 MHz NMR Spectrum of 3-Thiabicyclo[3.1.1]heptane (121) in CCl_4. (500 Hz Sweep Width).

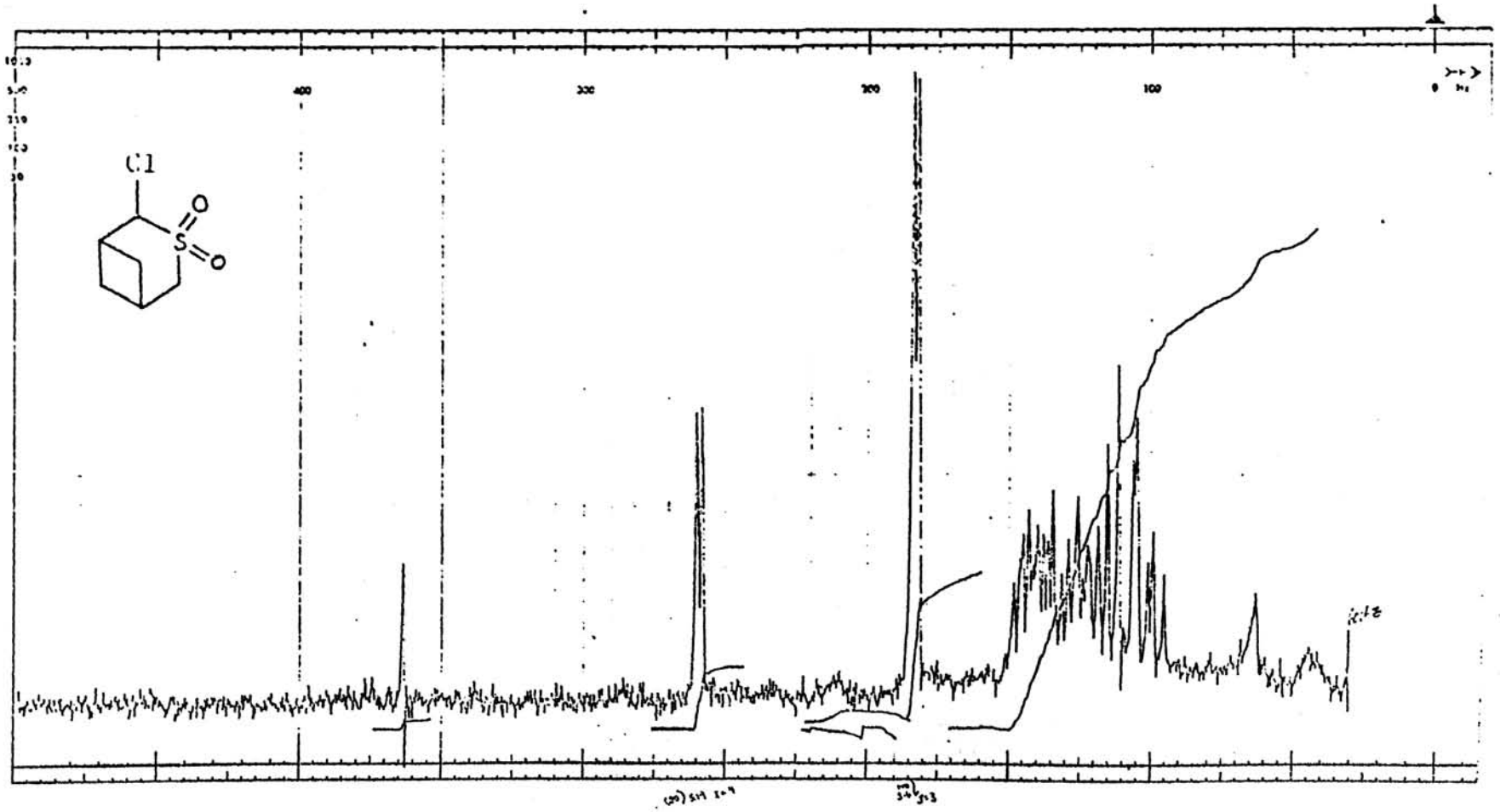

Fig. 24. 100 MHz NMR Spectrum of 2-Chloro-3-thiabicyclo[3.1.1]heptane 3,3-Dioxide (122) in $CDCl_3$. (1000 Hz Sweep Width).

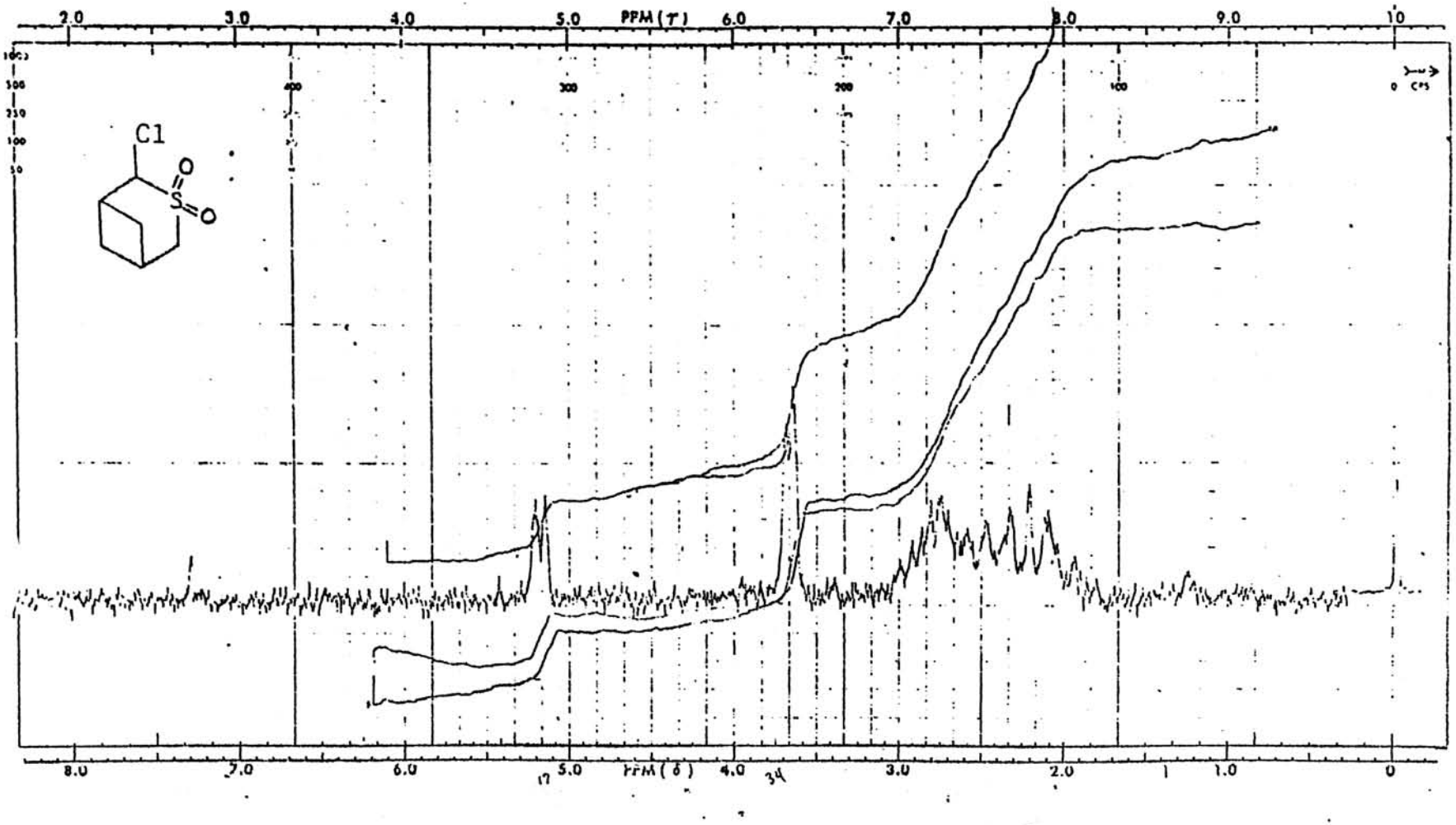

Fig. 25. 60 MHz NMR Spectrum of 2-Chloro-3-thiabicyclo[3.1.1]heptane 3,3-Dioxide (122) in $CDCl_3$. (500 Hz Sweep Width).

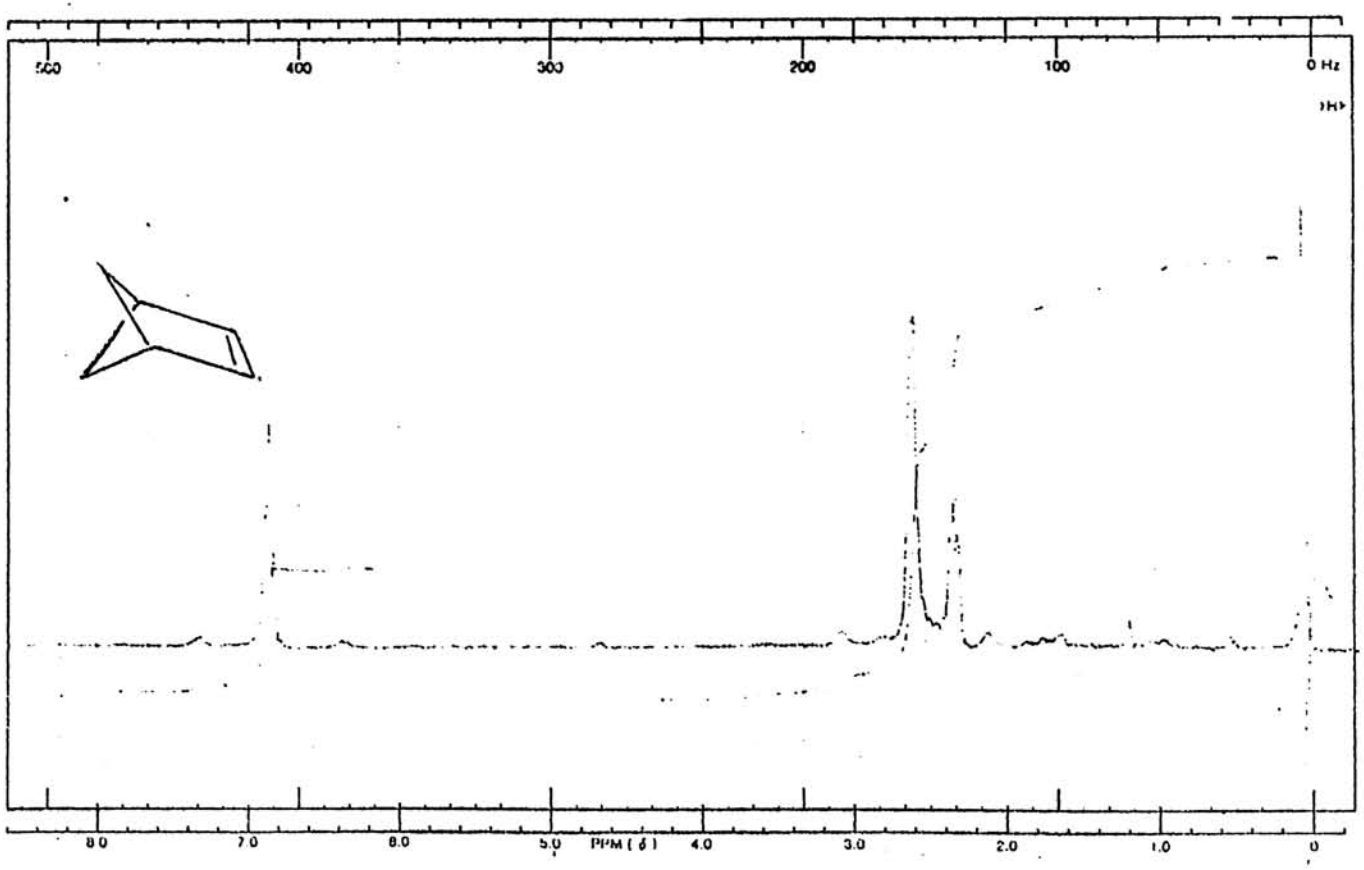

Fig. 26. 60 MHz NMR Spectrum of Bicyclo[2.1.1]hex-2-ene (78) in CCl_4. (500 Hz Sweep Width).

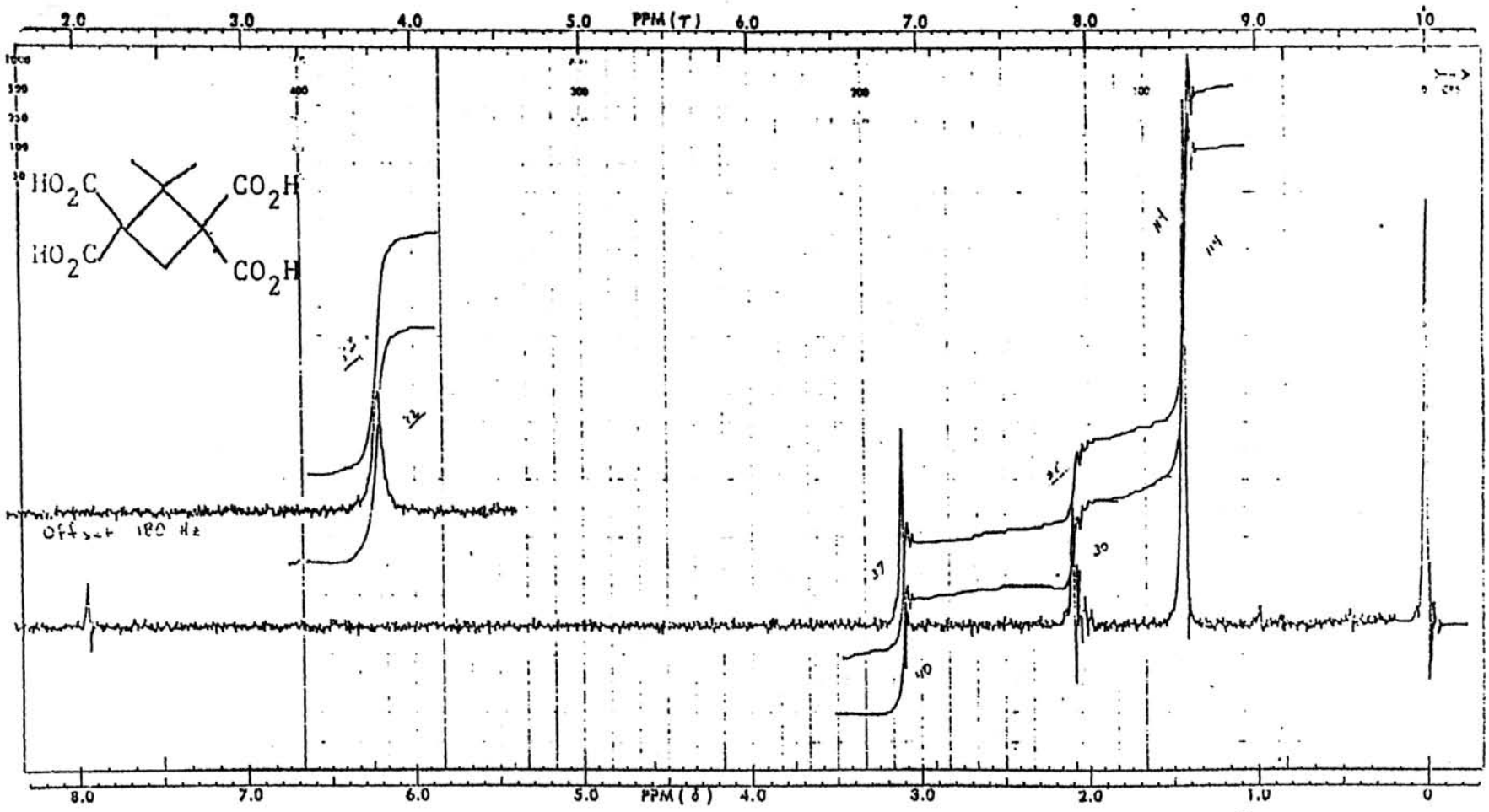

Fig. 27. 60 MHz NMR Spectrum of 2,2-Dimethyl-1,1,3,3-cyclobutanetetracarboxylic Acid (127) in Acetone-d_6. (500 Hz Sweep Width).

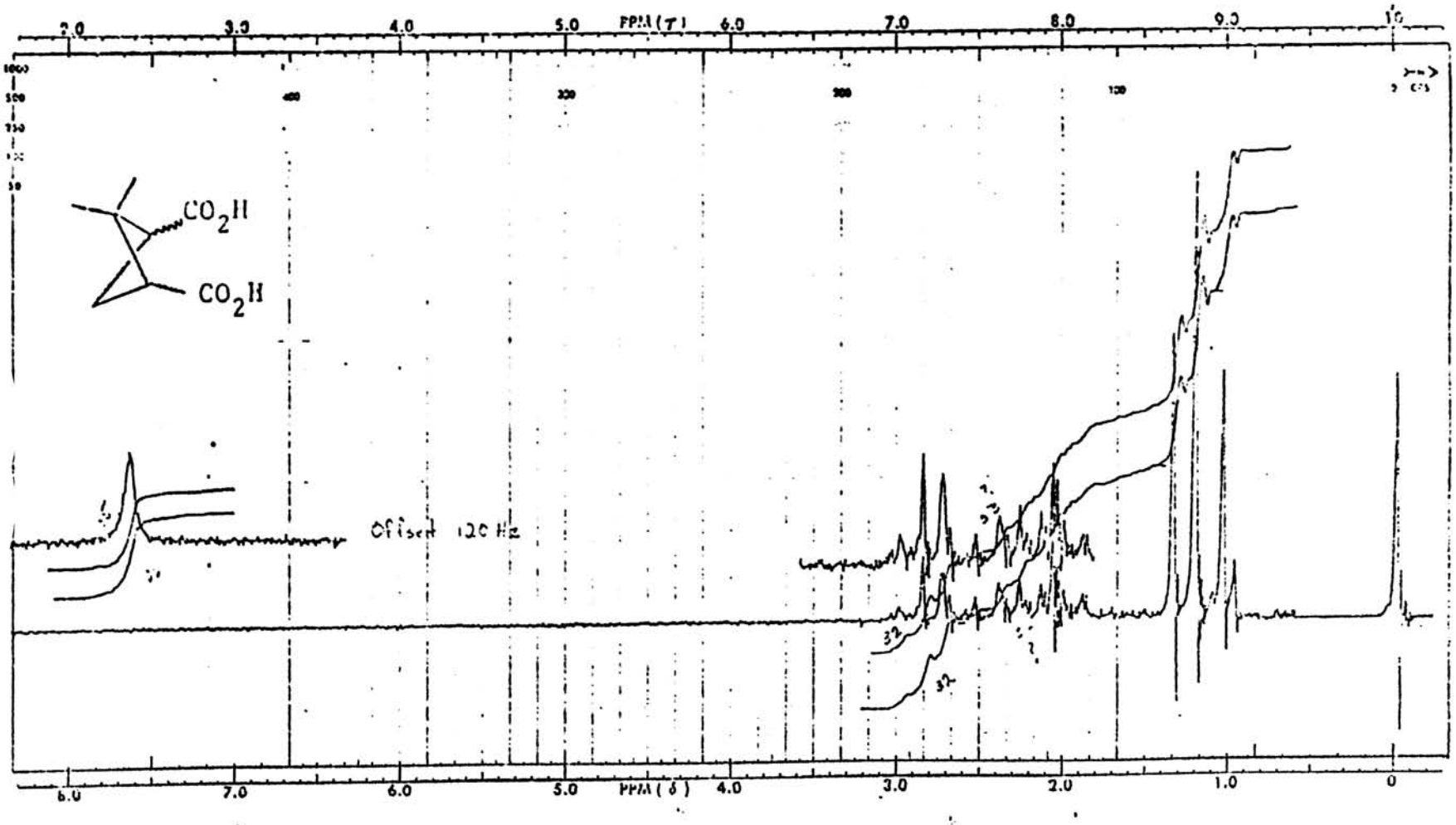

Fig. 28. 60 MHz NMR Spectrum of Norpinic Acid (128) in Acetone-d_6. (500 Hz Sweep Width).

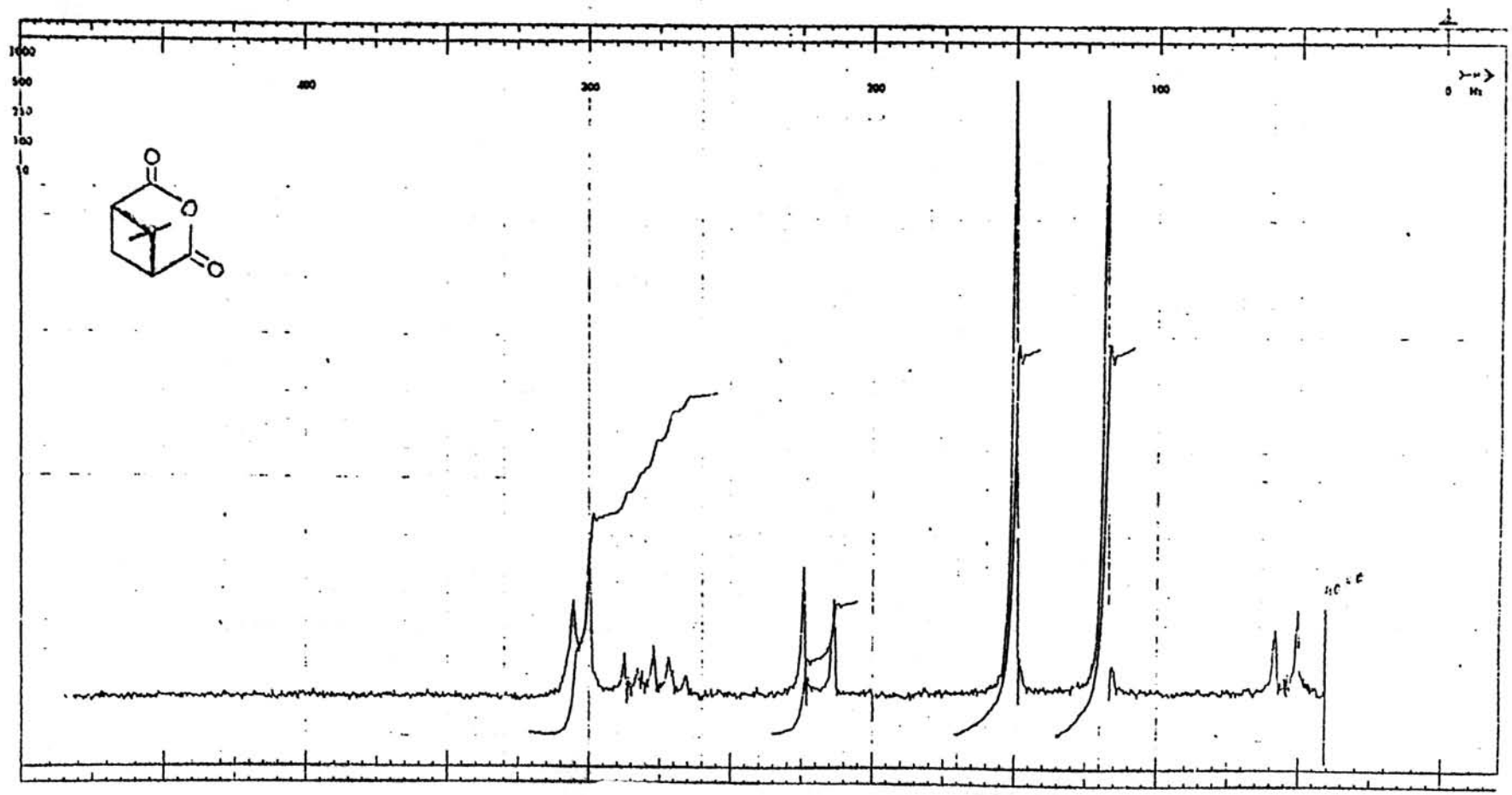

Fig. 29. 100 MHz NMR Spectrum of Norpinic Anhydride (129) in $CDCl_3$. (500 Hz Sweep Width).

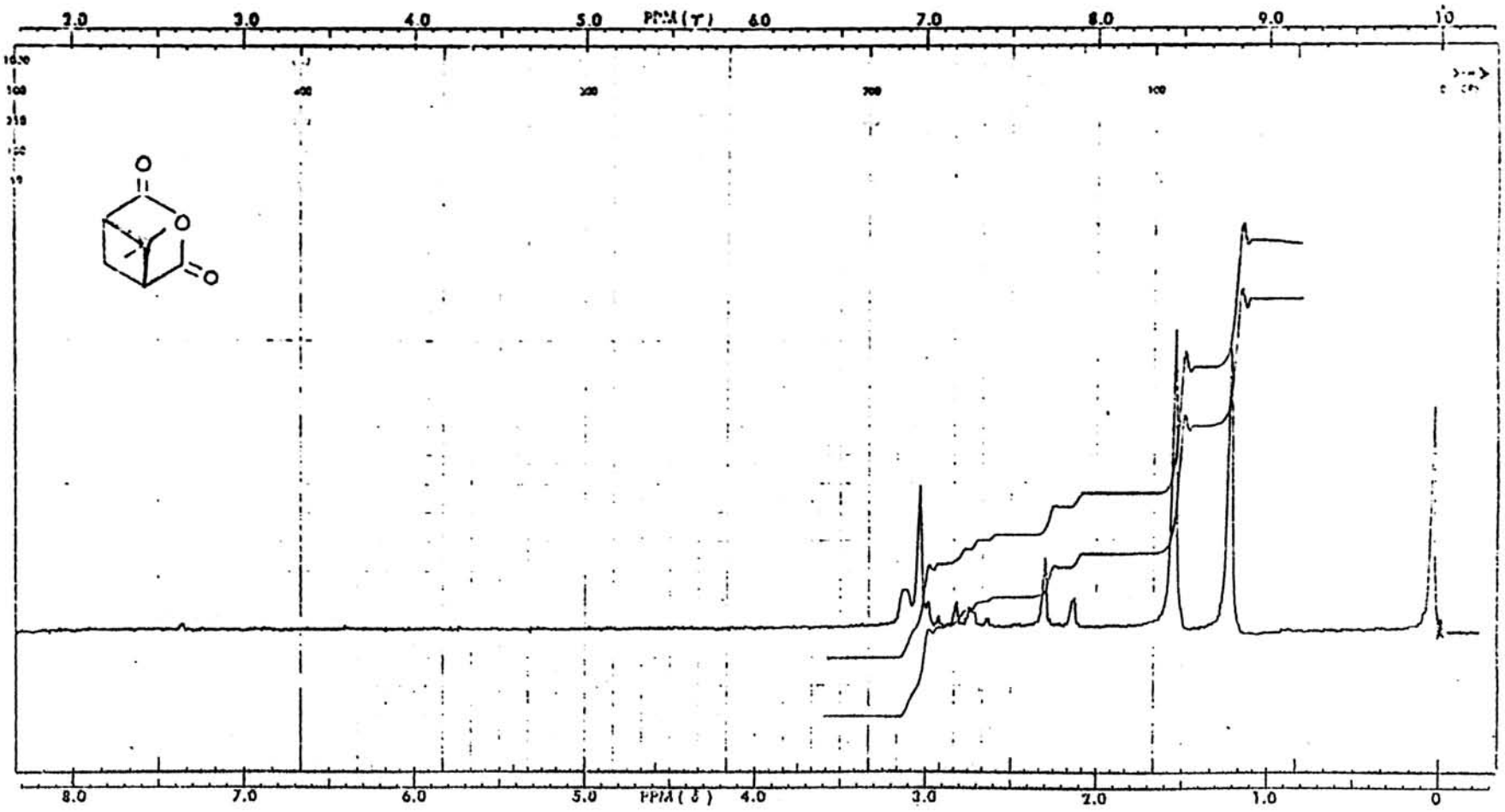

Fig. 30. 60 MHz NMR Spectrum of Norpinic Anhydride (129) in $CDCl_3$. (500 Hz Sweep Width).

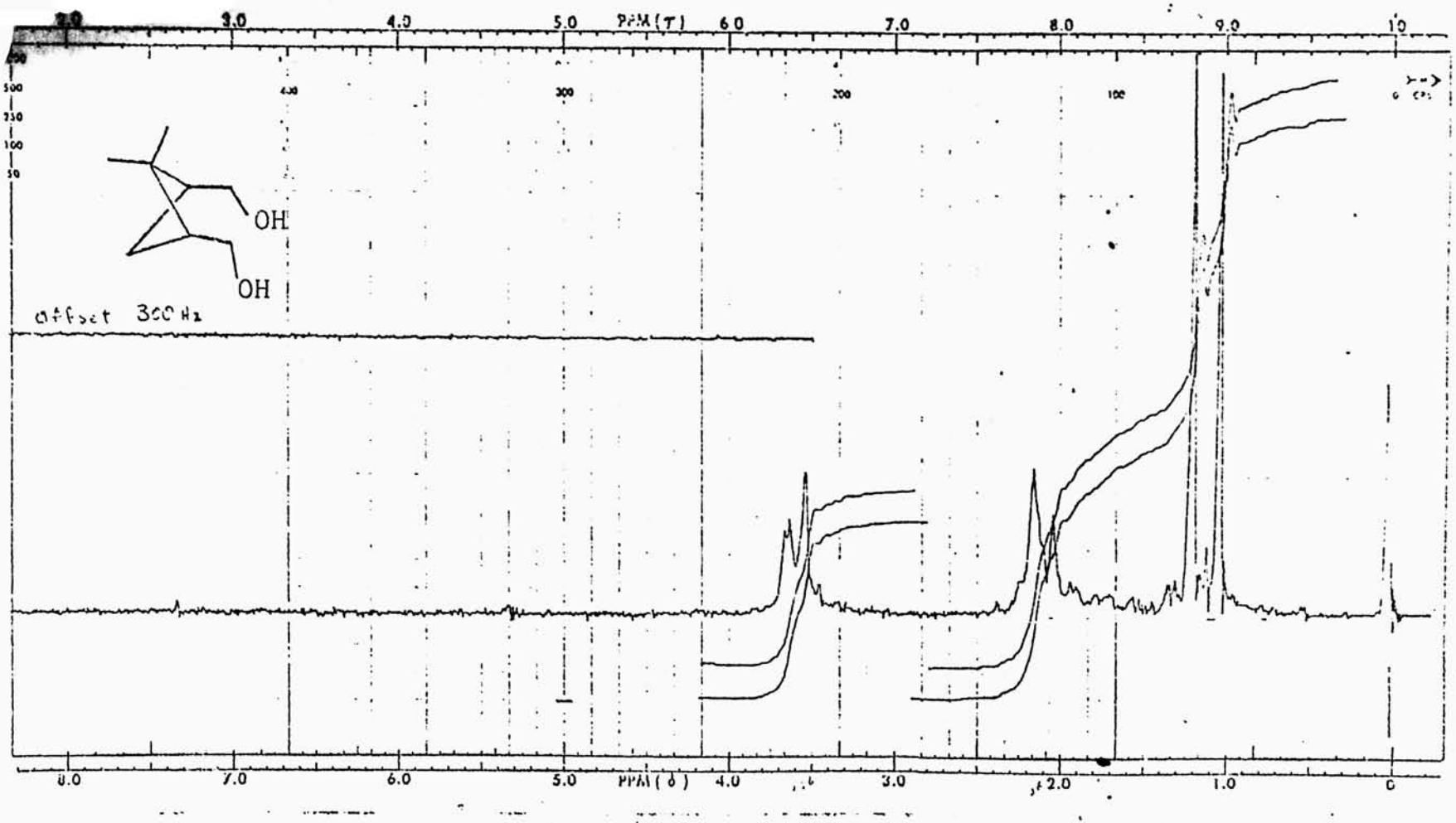

Fig. 31. 60 MHz NMR Spectrum of cis-1,3-Bis(hydroxymethyl)-2,2-dimethylcyclobutane (130) in $CDCl_3$. (500 Hz Sweep Width).

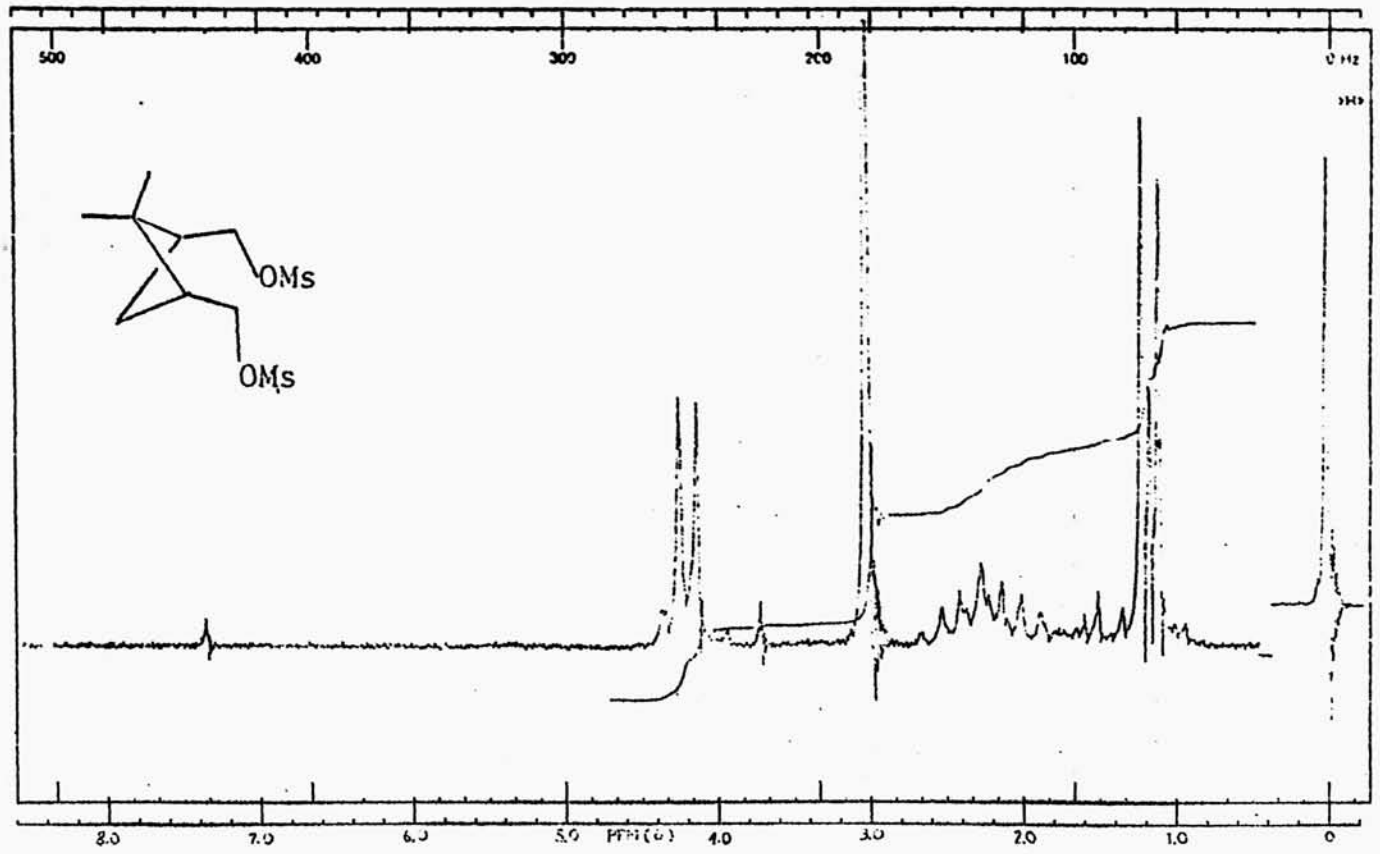

Fig. 32. 60 MHz NMR Spectrum of the Dimesylate of cis-1,3-Bis(hydroxymethyl)-2,2-dimethylcyclobutane (131) in $CDCl_3$. (500 Hz Sweep Width).

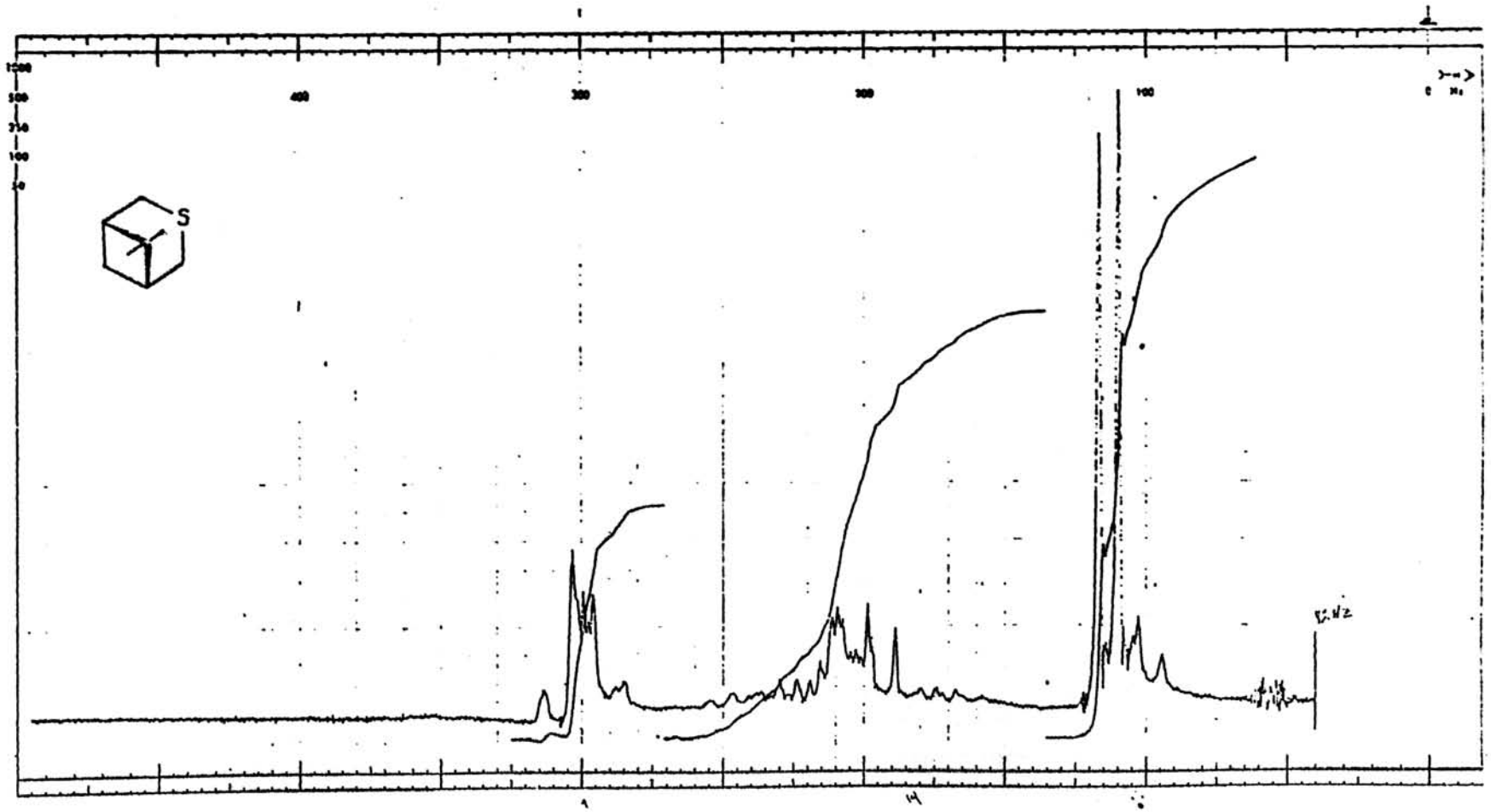

Fig. 33. 100 MHz NMR Spectrum of 6,6-Dimethyl-3-thiabicyclo[3.1.1]heptane (132) in CCl_4. (500 Hz Sweep Width).

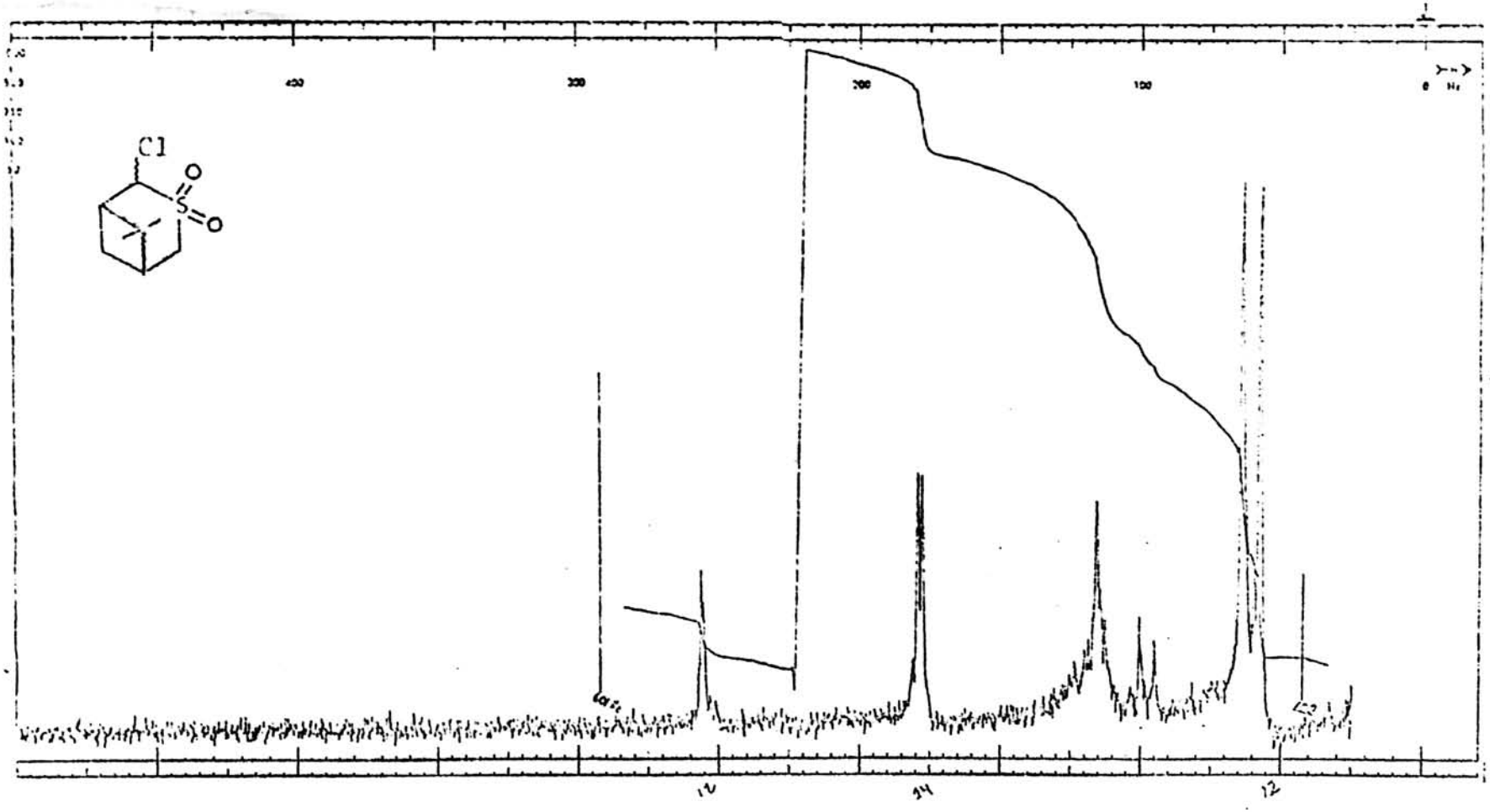

Fig. 34. 100 MHz NMR Spectrum of 2-Chloro-6,6-dimethyl-3-thiabicyclo[3.1.1]heptane 3,3-Dioxide (125) in $CDCl_3$. (1000 Hz Sweep Width).

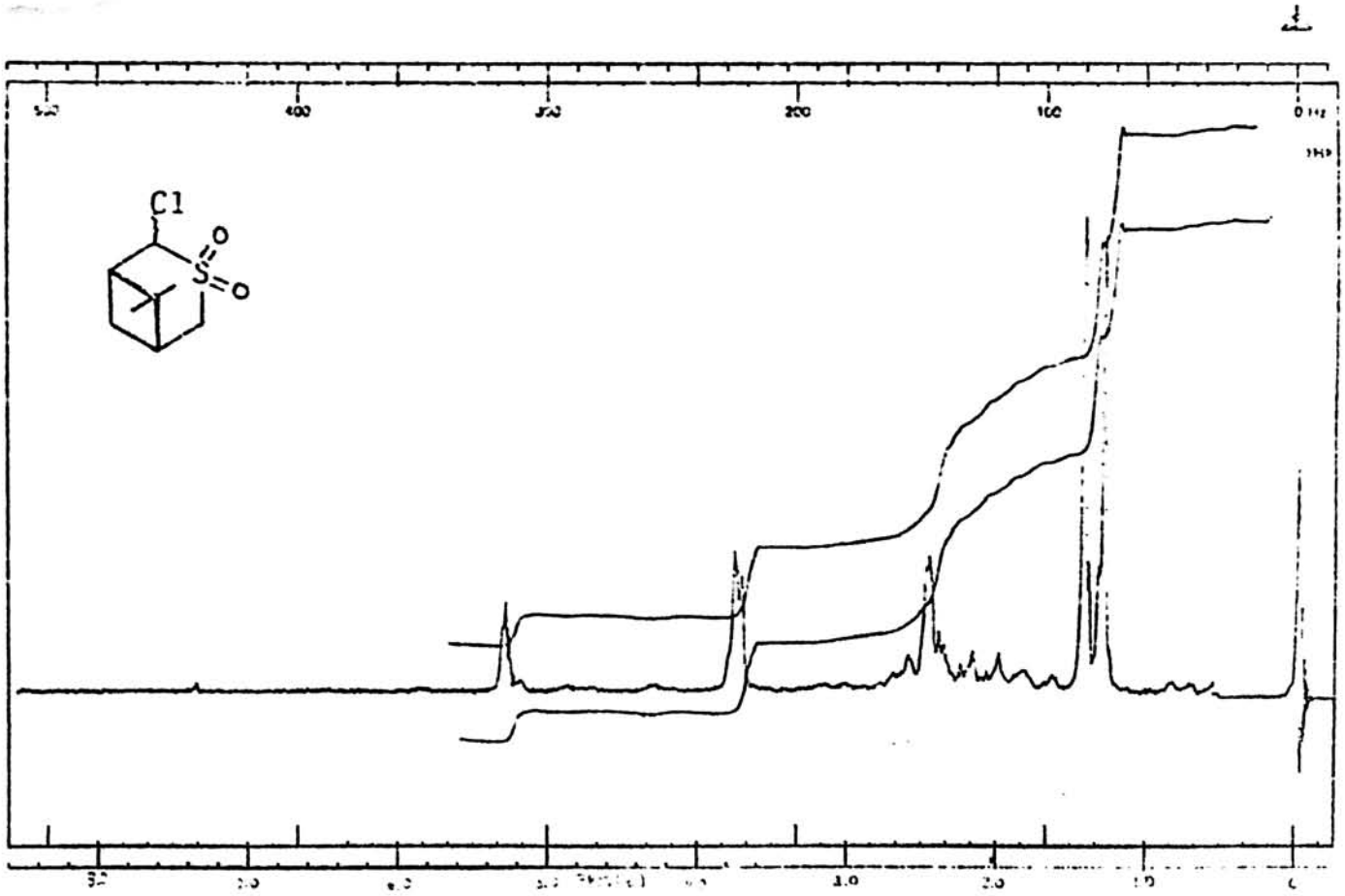

Fig. 35. 60 MHz NMR Spectrum of 2-Chloro-3-thiabicyclo[3.1.1]heptane 3,3-Dioxide (125) in $CDCl_3$. (500 Hz Sweep Width).

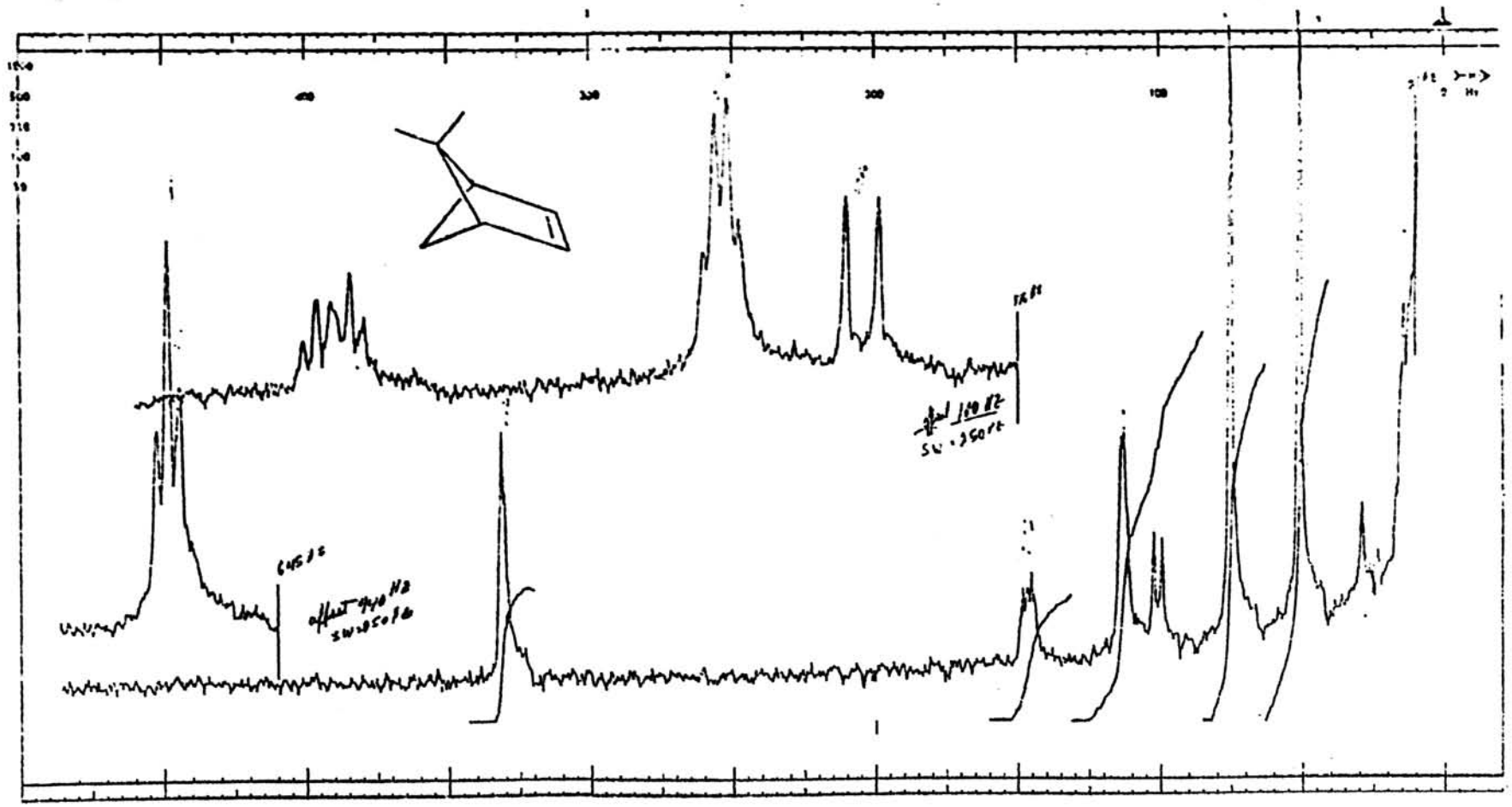

Fig. 36. 100 MHz NMR Spectrum of 5,5-Dimethylbicyclo[2.1.1]hex-2-ene (126) in CCl_4. (1000 Hz Sweep Width).

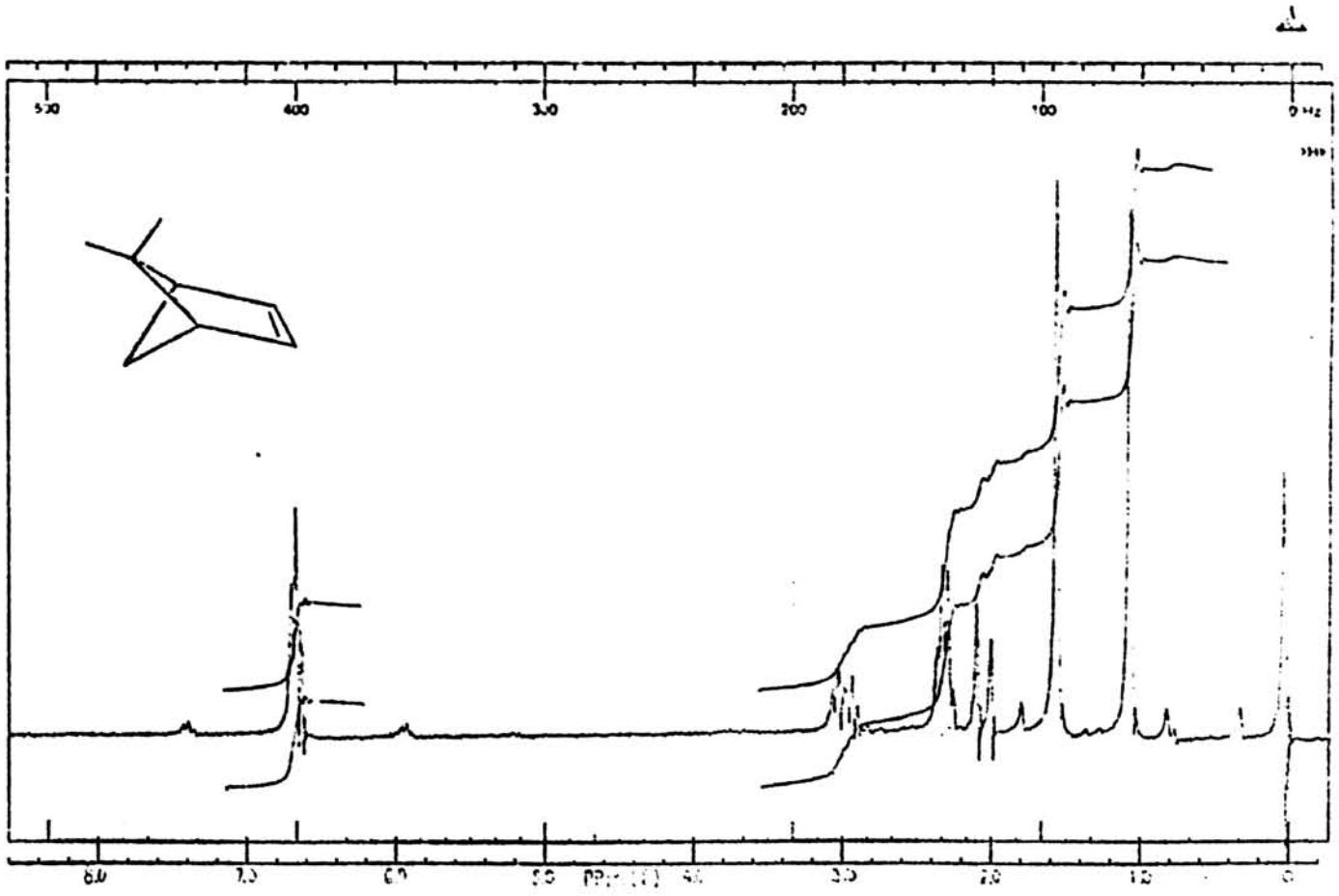

Fig. 37. 60 MHz NMR Spectrum of 5,5-Dimethylbicyclo[2.1.1]hex-2-ene (126) in CCl_4. (500 Hz Sweep Width).

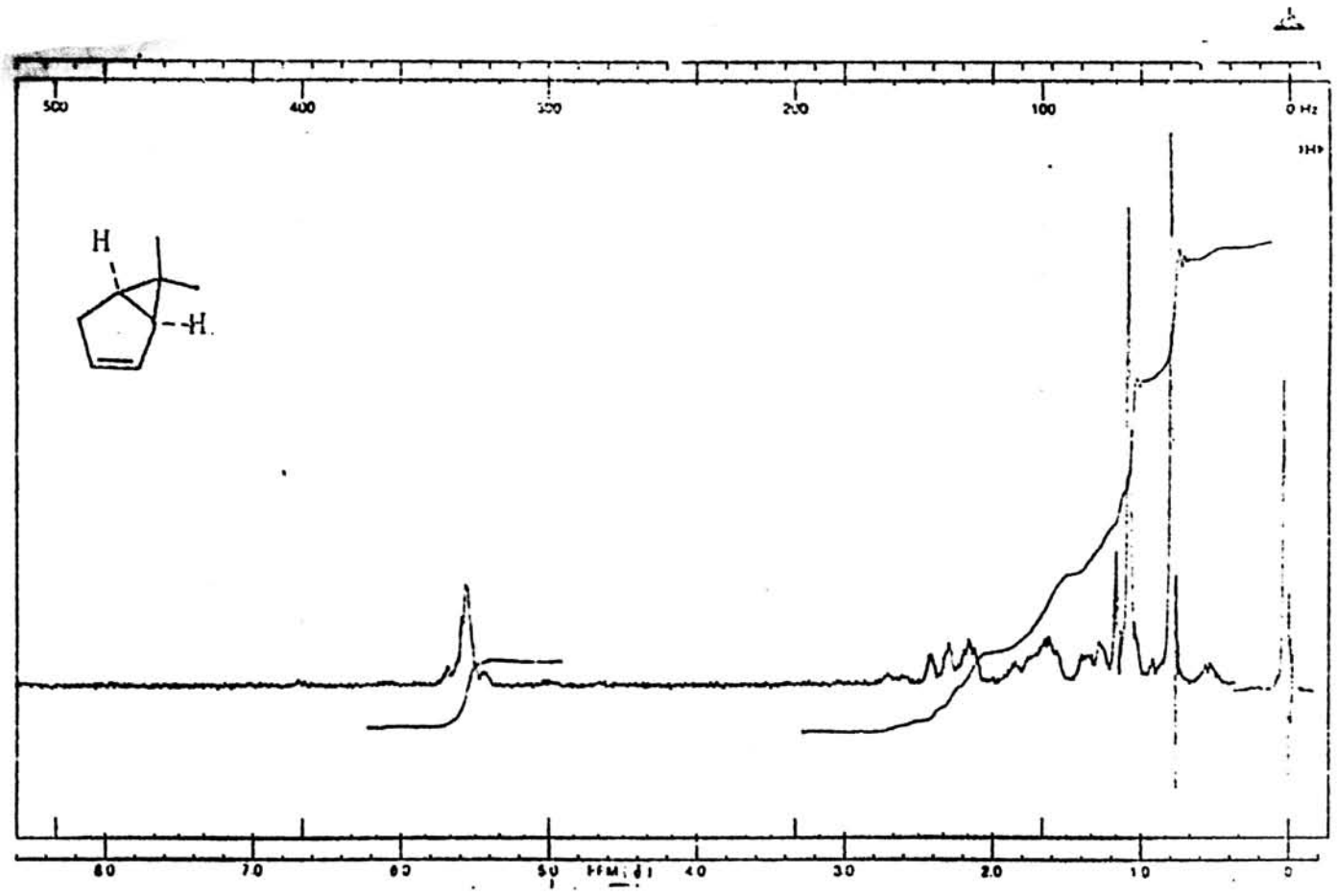

Fig. 38. 60 MHz NMR Spectrum of 6,6-Dimethylbicyclo[3.1.0]hex-2-ene (133) in CCl_4. (500 Hz Sweep Width).

INFRARED SPECTRA

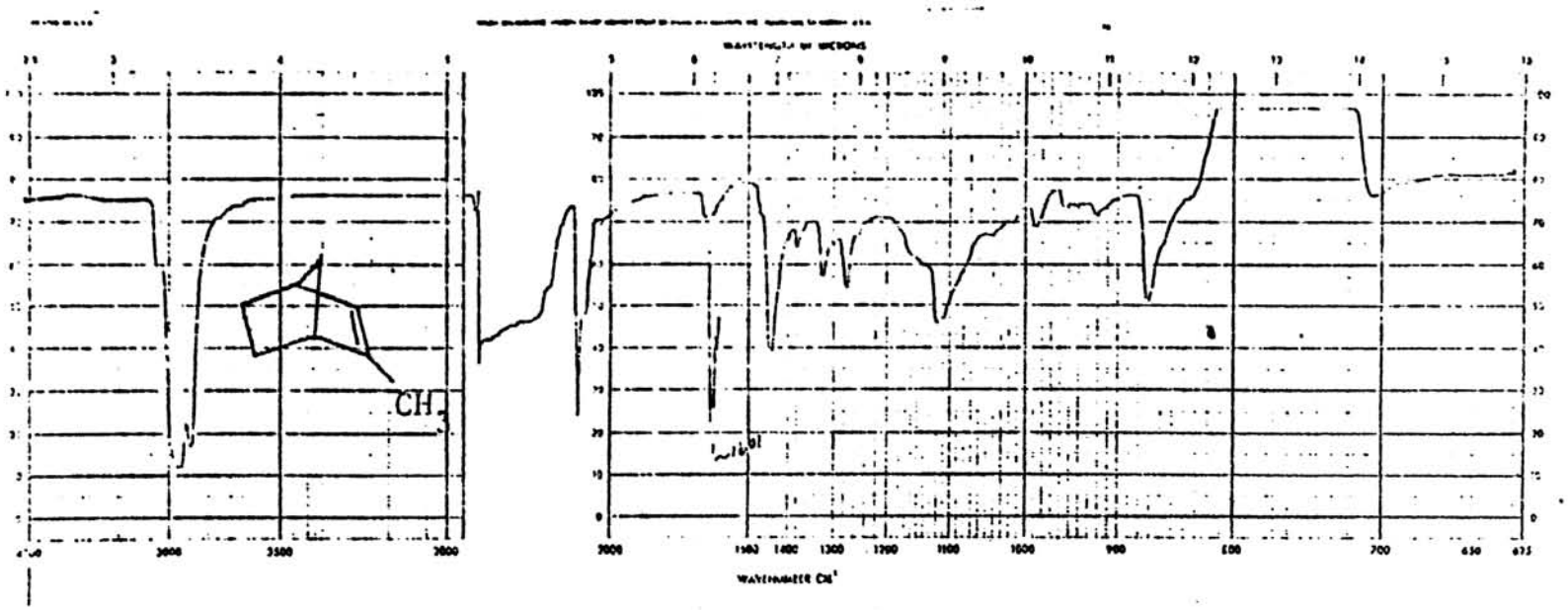

Fig. 39. IR Spectrum of 2-Methylnorbornene (81). (3% in CCl_4).

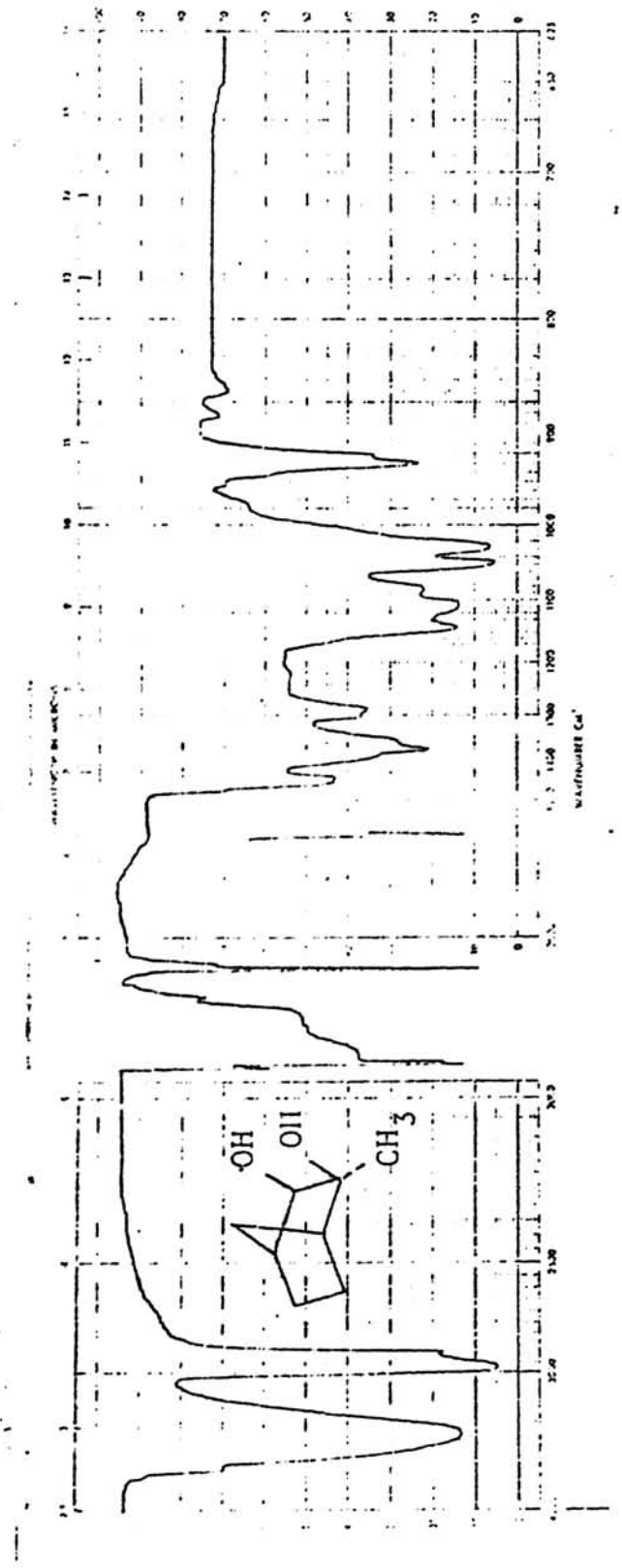

Fig. 40. IR Spectrum of 2-endo-Methyl-2,3-cis,exo-norbornanediol (80). (3% in CCl_4).

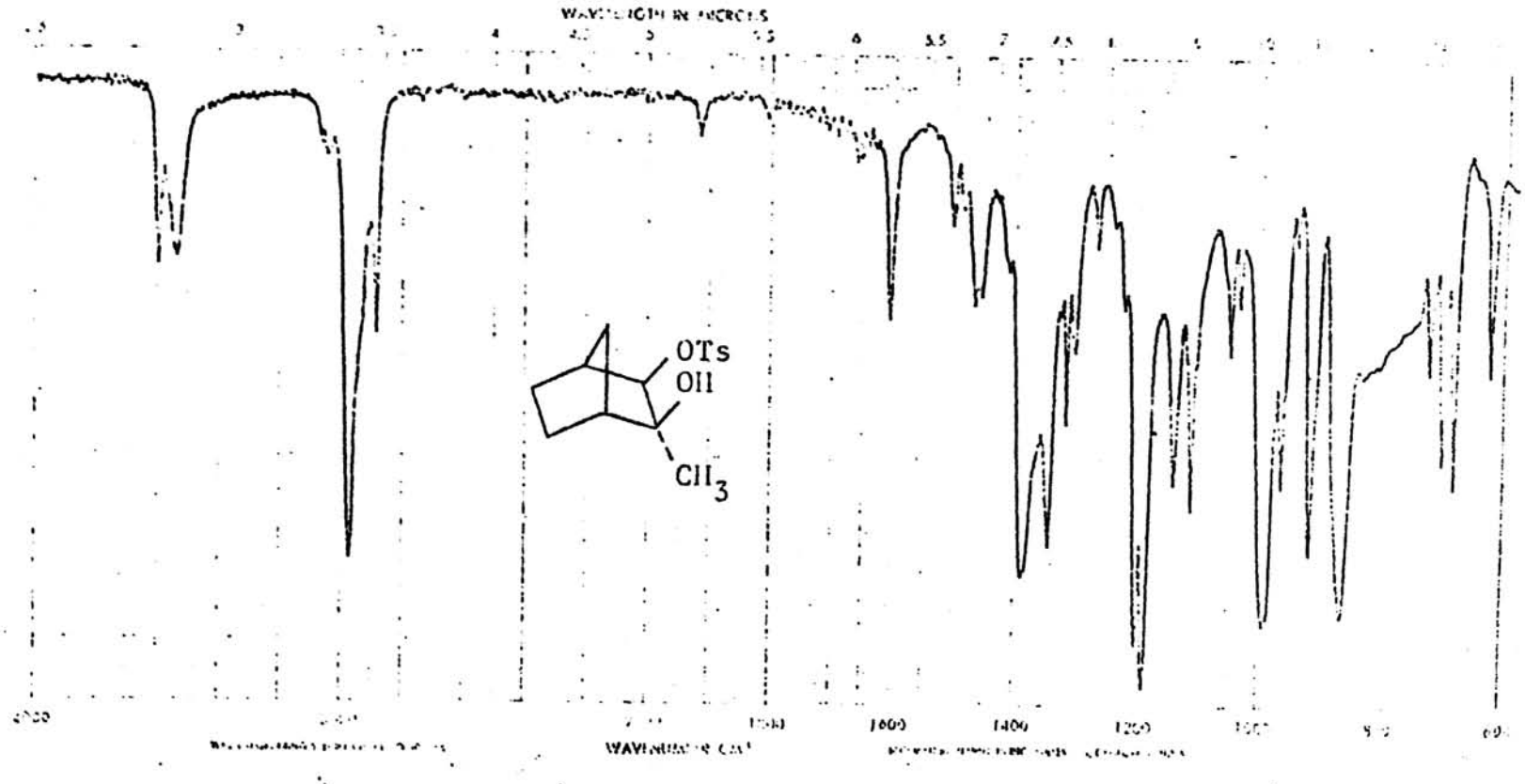

Fig. 41. IR Spectrum of 2-endo-Methyl-2,3-cis,exo-norbornanediol 3-p-Toluenesulfonate (20). (1.5% in CCl_4).

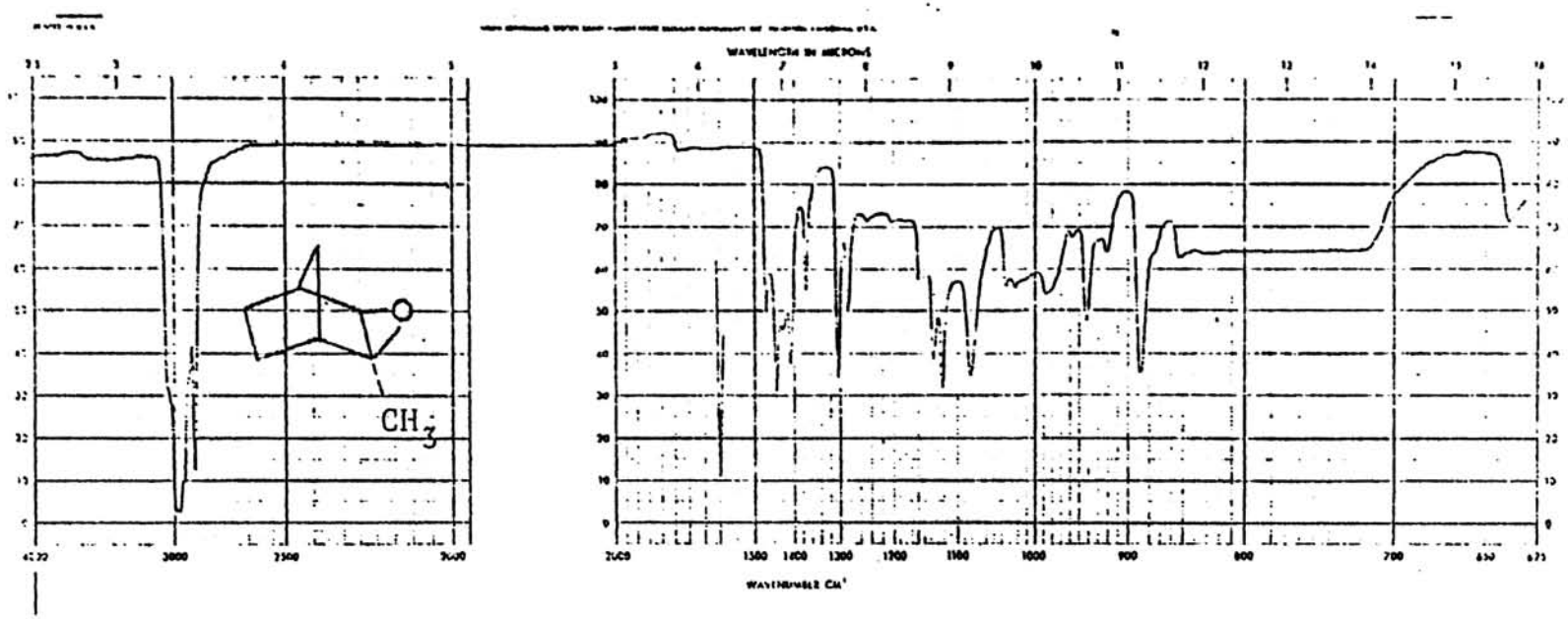

Fig. 42. IR Spectrum of 2-endo-Methyl-exo-epoxynorbornane (87). (2.3% in CCl_4).

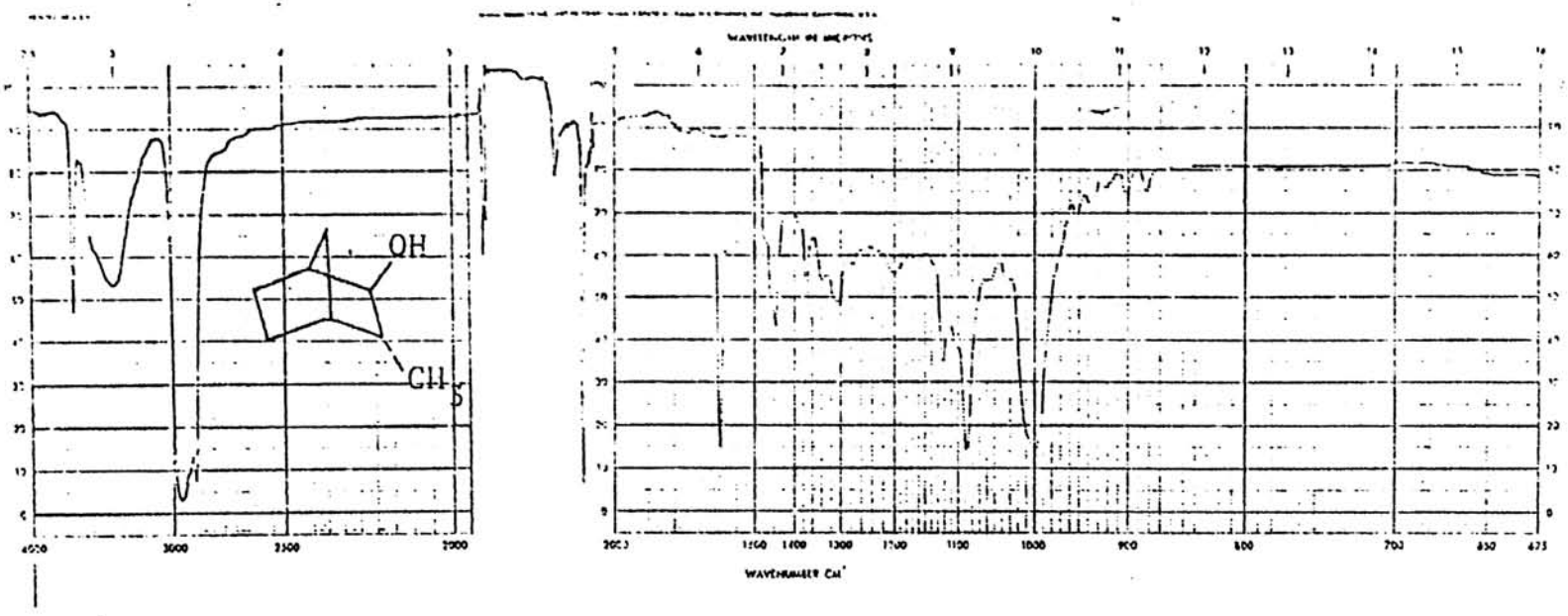

Fig. 43. IR Spectrum of 3-endo-Methyl-2-exo-norbornanol (93). (4% in CCl_4).

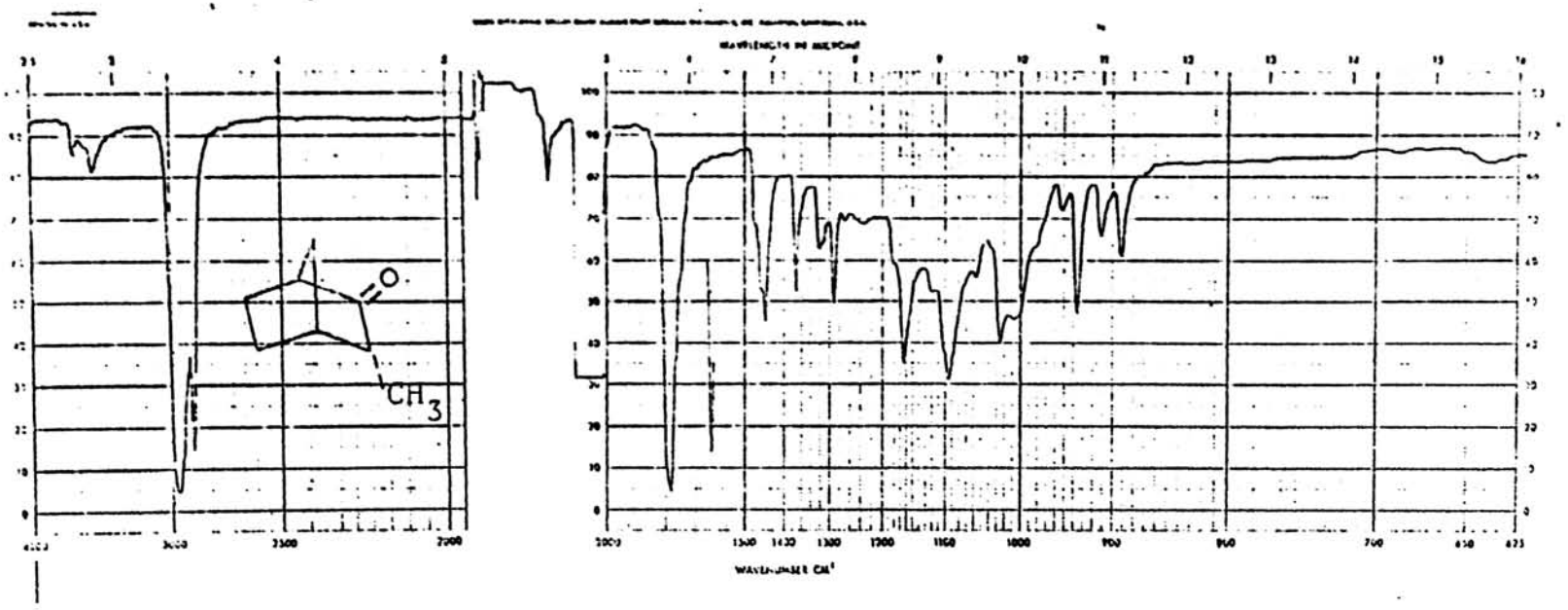

Fig. 44. IR Spectrum of 3-endo-Methylbicyclo[2.2.1]hept-2-one (94). (4% in CCl_4).

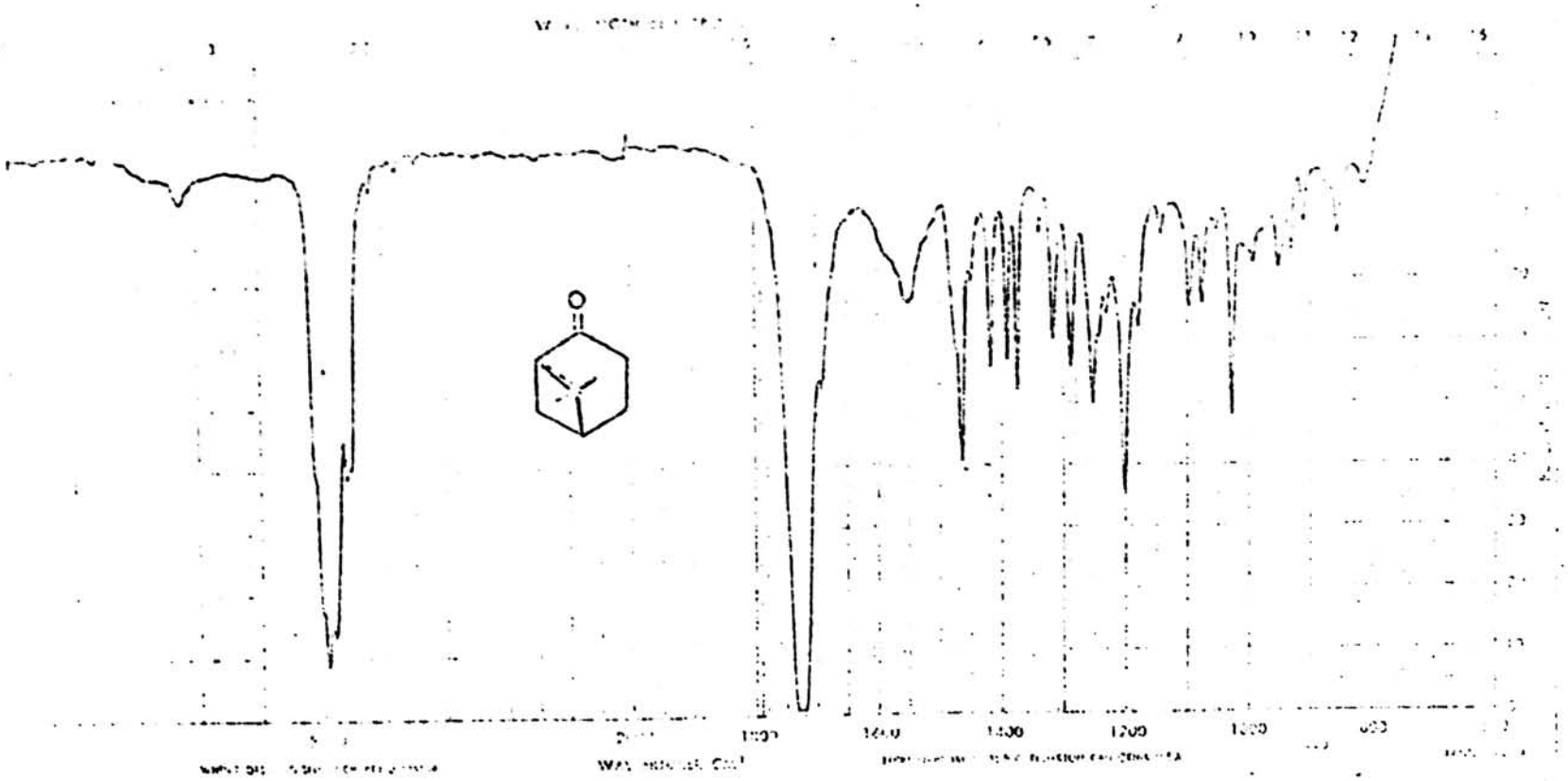

Fig. 45. IR Spectrum of Nopinone (108). (3% in CCl_4).

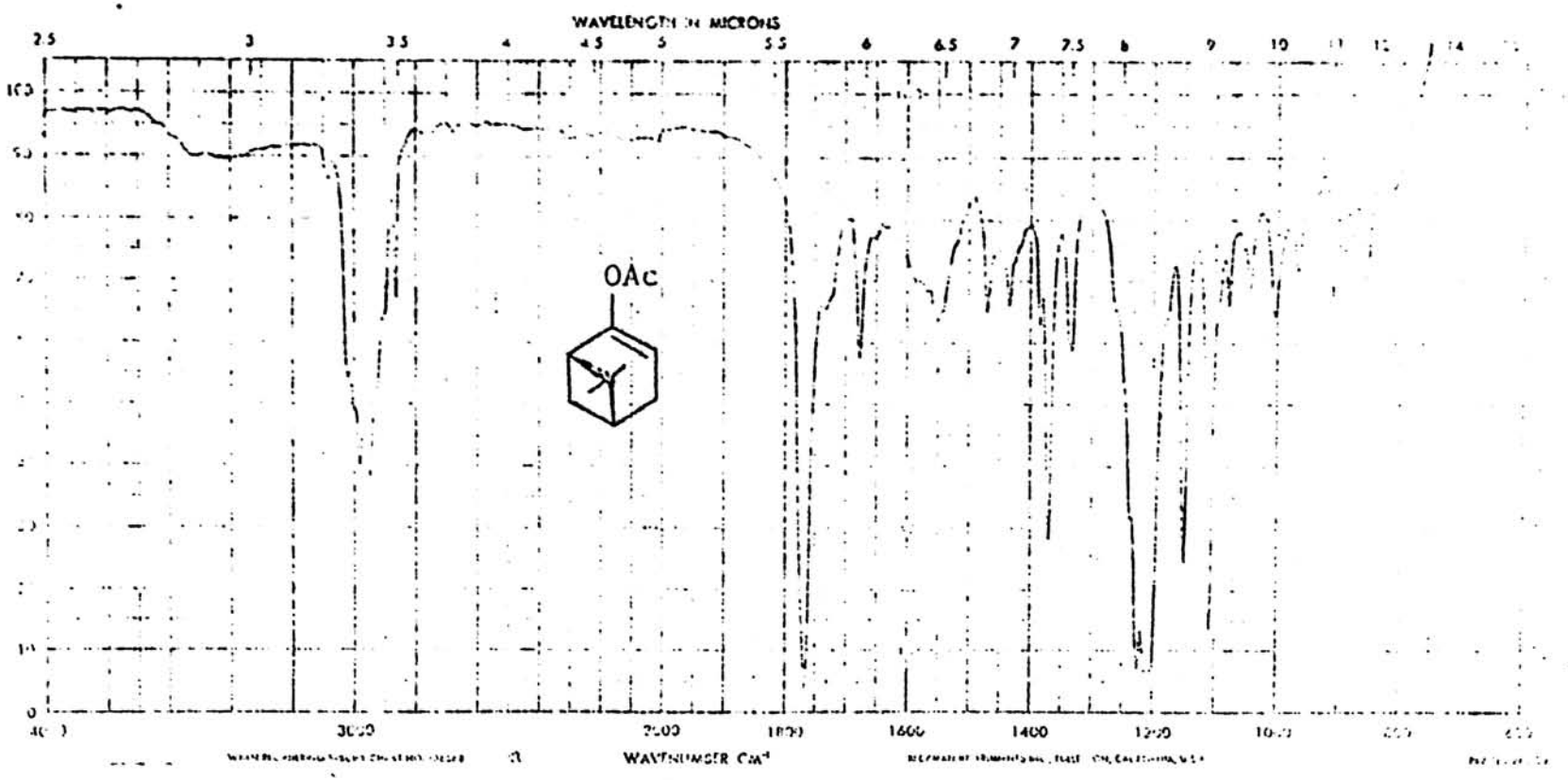

Fig. 46. IR Spectrum of 2-Acetoxypin-2-ene (109). (2% in CCl_4)

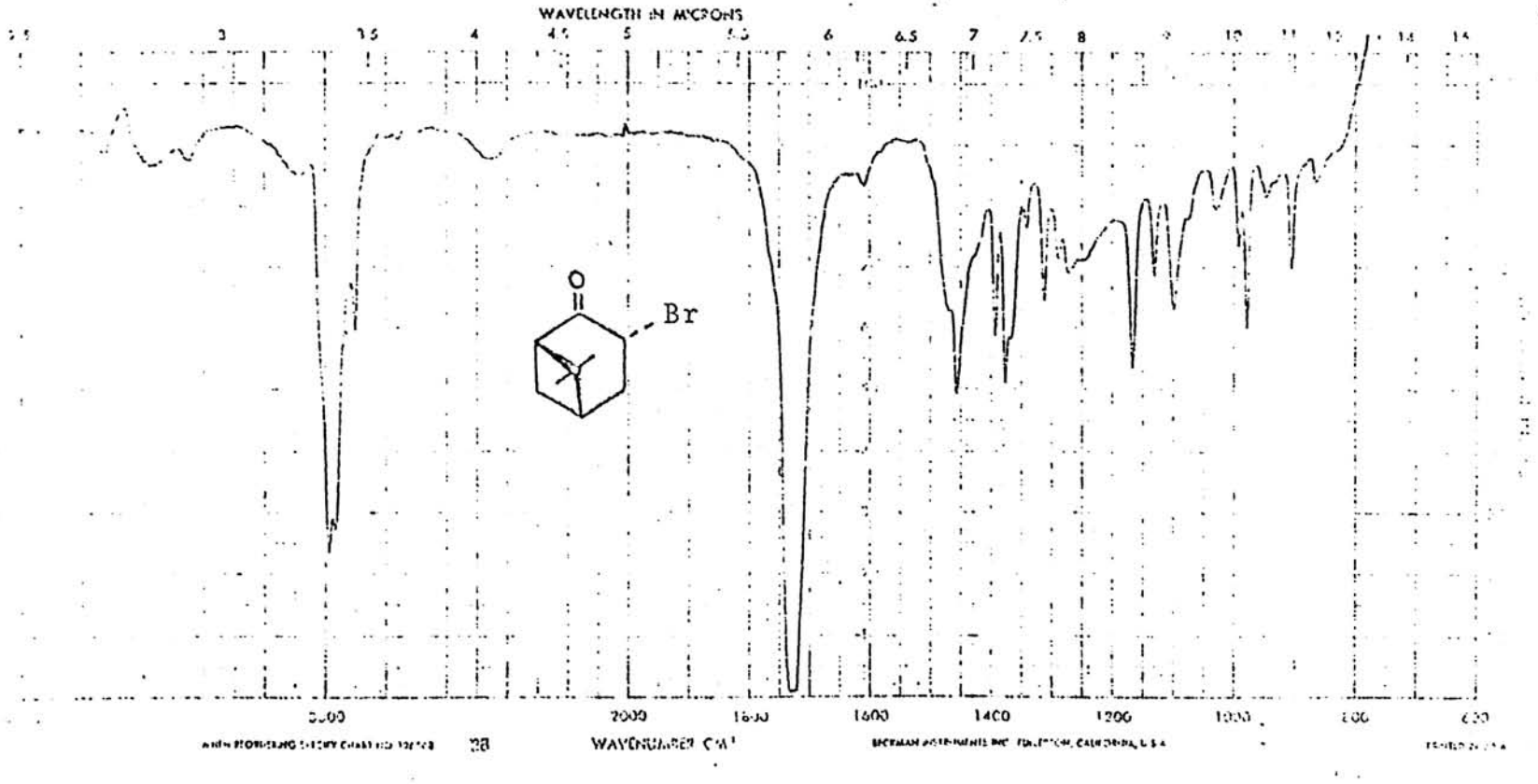

Fig. 47. IR Spectrum of 3-α-Bromonopinone (110a). (1.7% in $CHCl_3$).

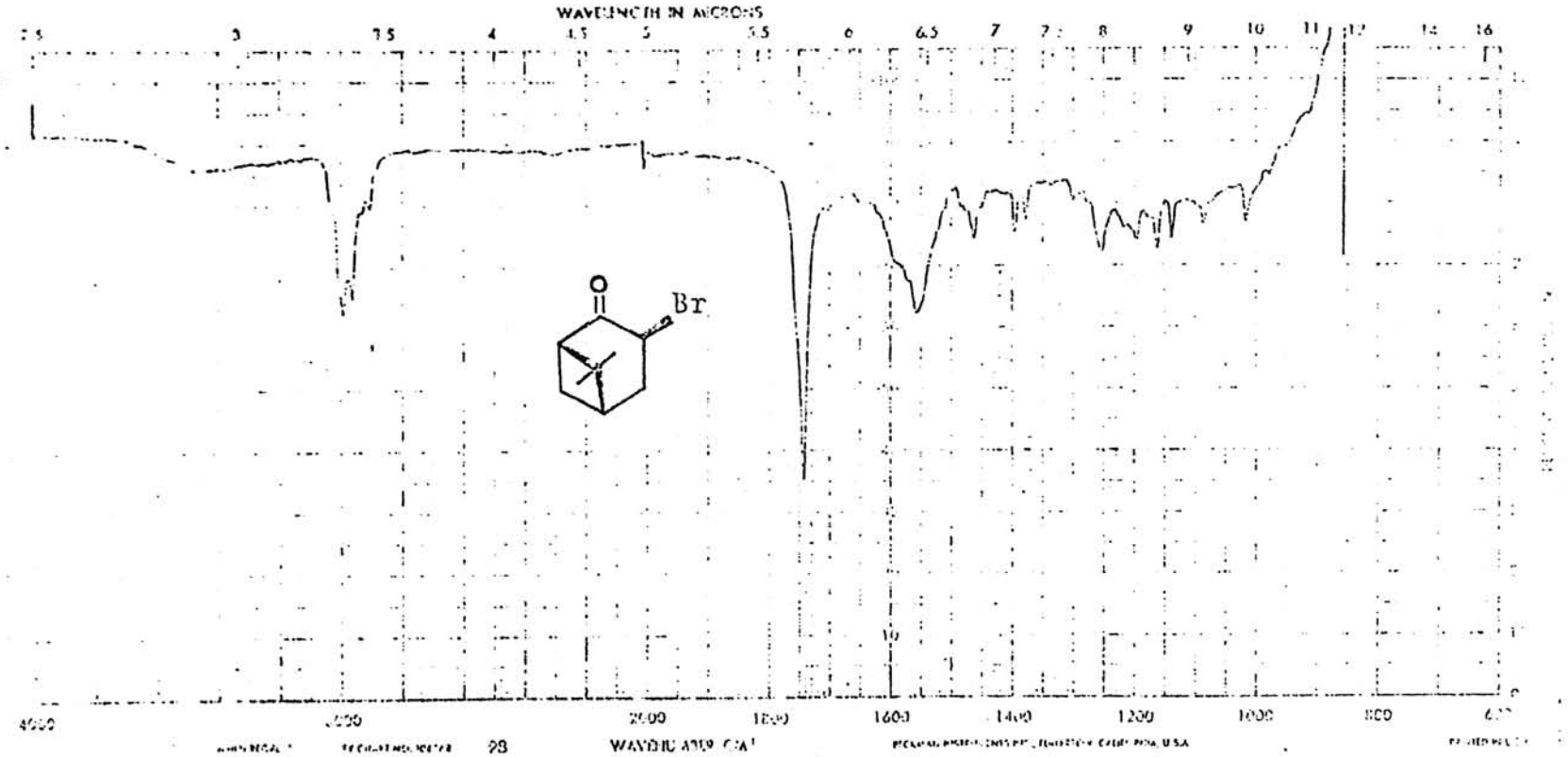

Fig. 48. IR Spectrum of 3-β-Bromonopinone (110b). (1% in CCl_4).

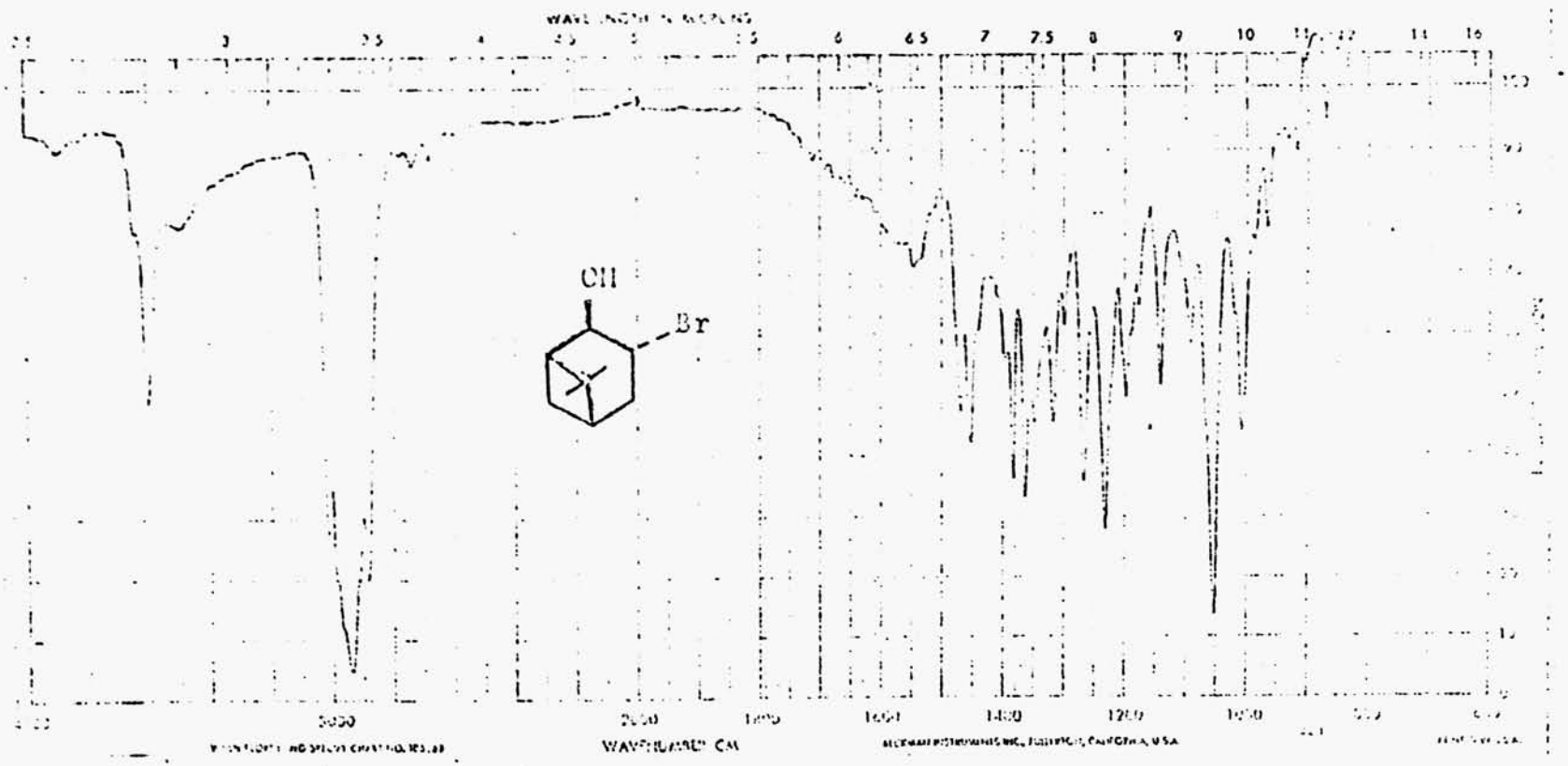

Fig. 49. IR Spectrum of 2-β-Hydroxy-3-α-bromopinane (35). (3% in CCl_4).

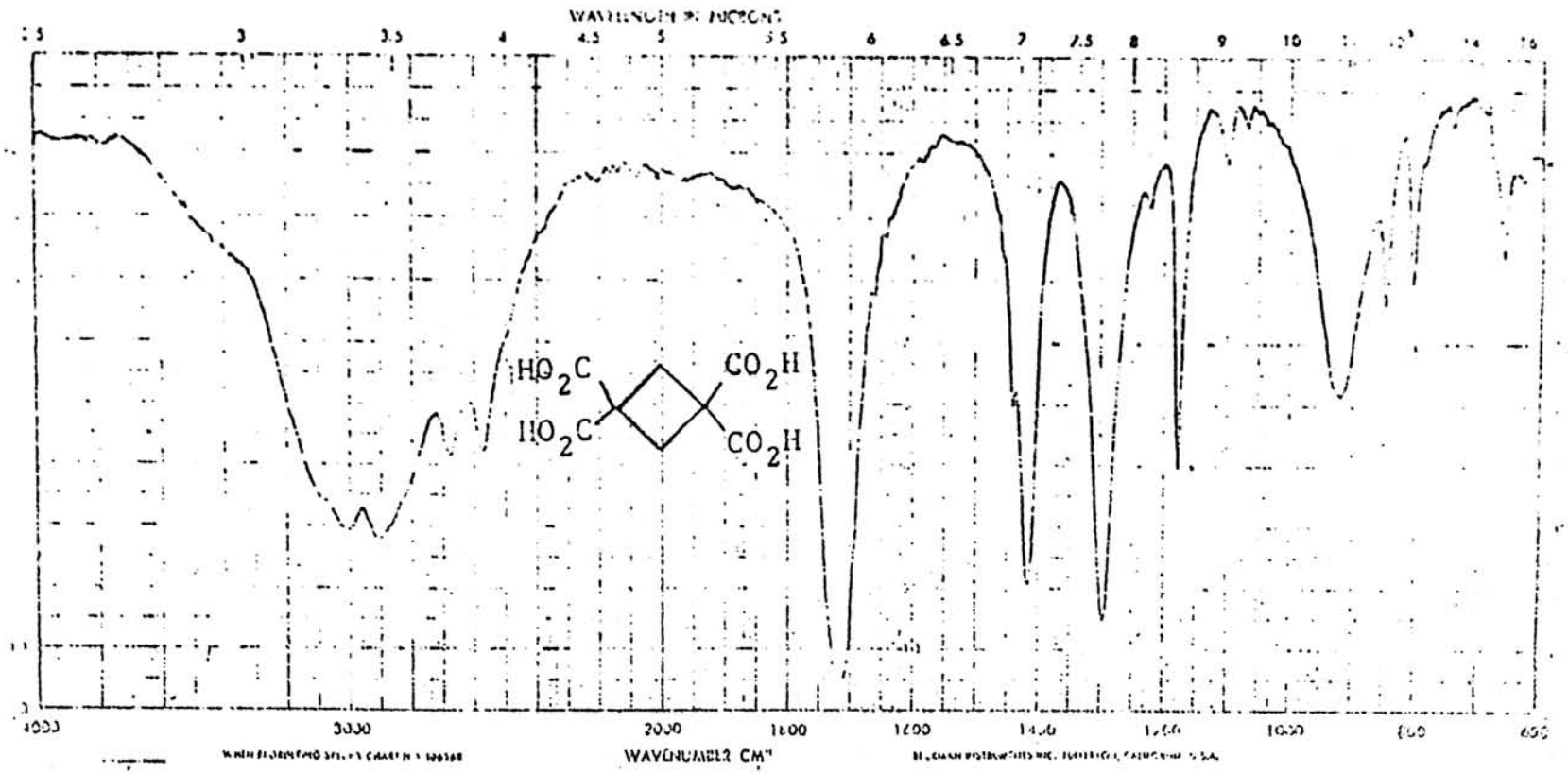

Fig. 50. IR Spectrum of 1,1,3,3-Cyclobutanetetracarboxylic Acid (116) (KBr Pellet).

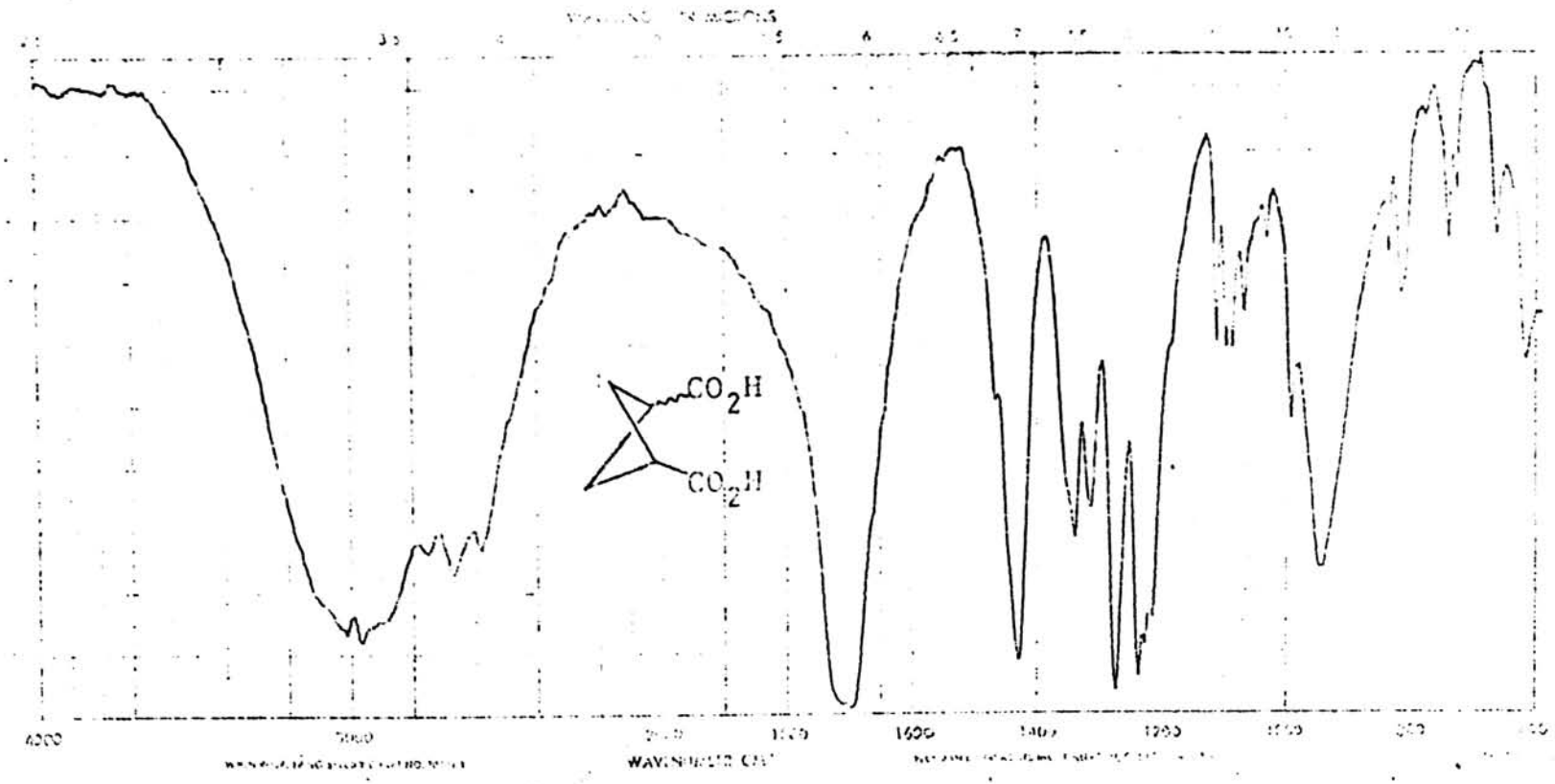

Fig. 51. IR Spectrum of cis-and trans-1,3-Cyclobutanedicarboxylic Acid (117a and 117b). (KBr Pellet).

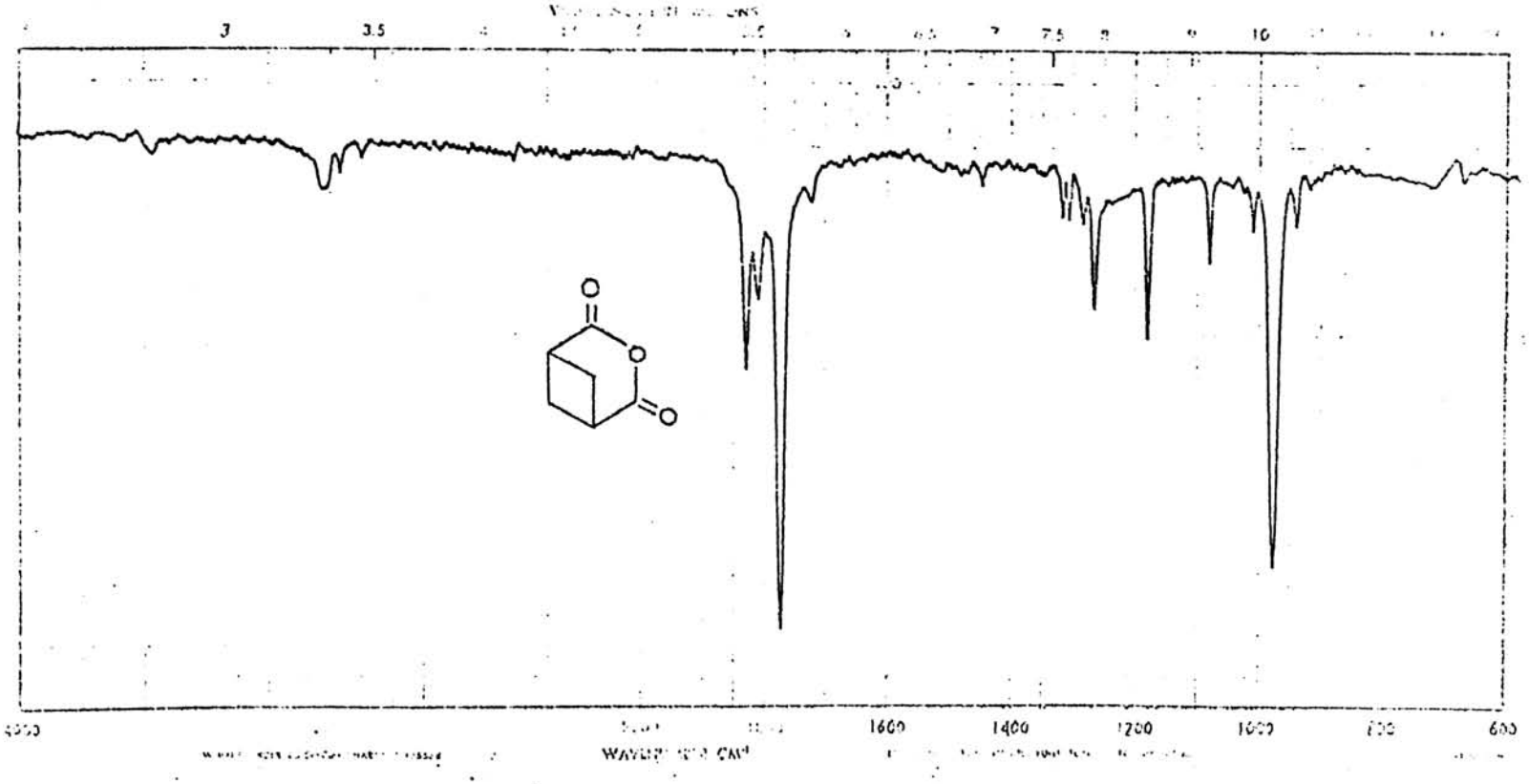

Fig. 52. IR Spectrum of cis-1,3-Cyclobutanedicarboxylic Acid Anhydride (118). (1% in $CHCl_3$).

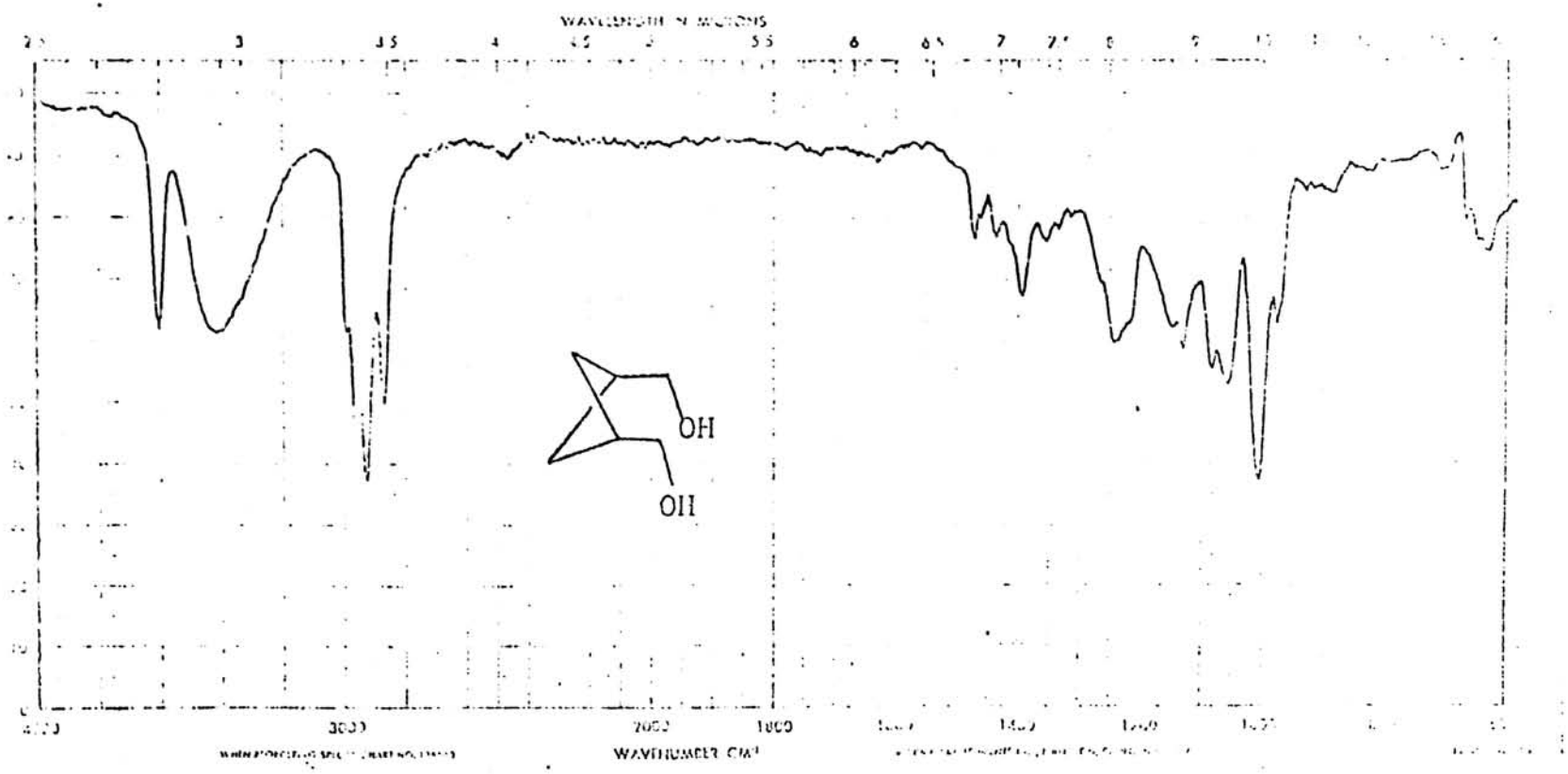

Fig. 53. IR Spectrum of cis-1,3-Bis(hydroxymethyl)cyclobutane (119). (3% in $CHCl_3$).

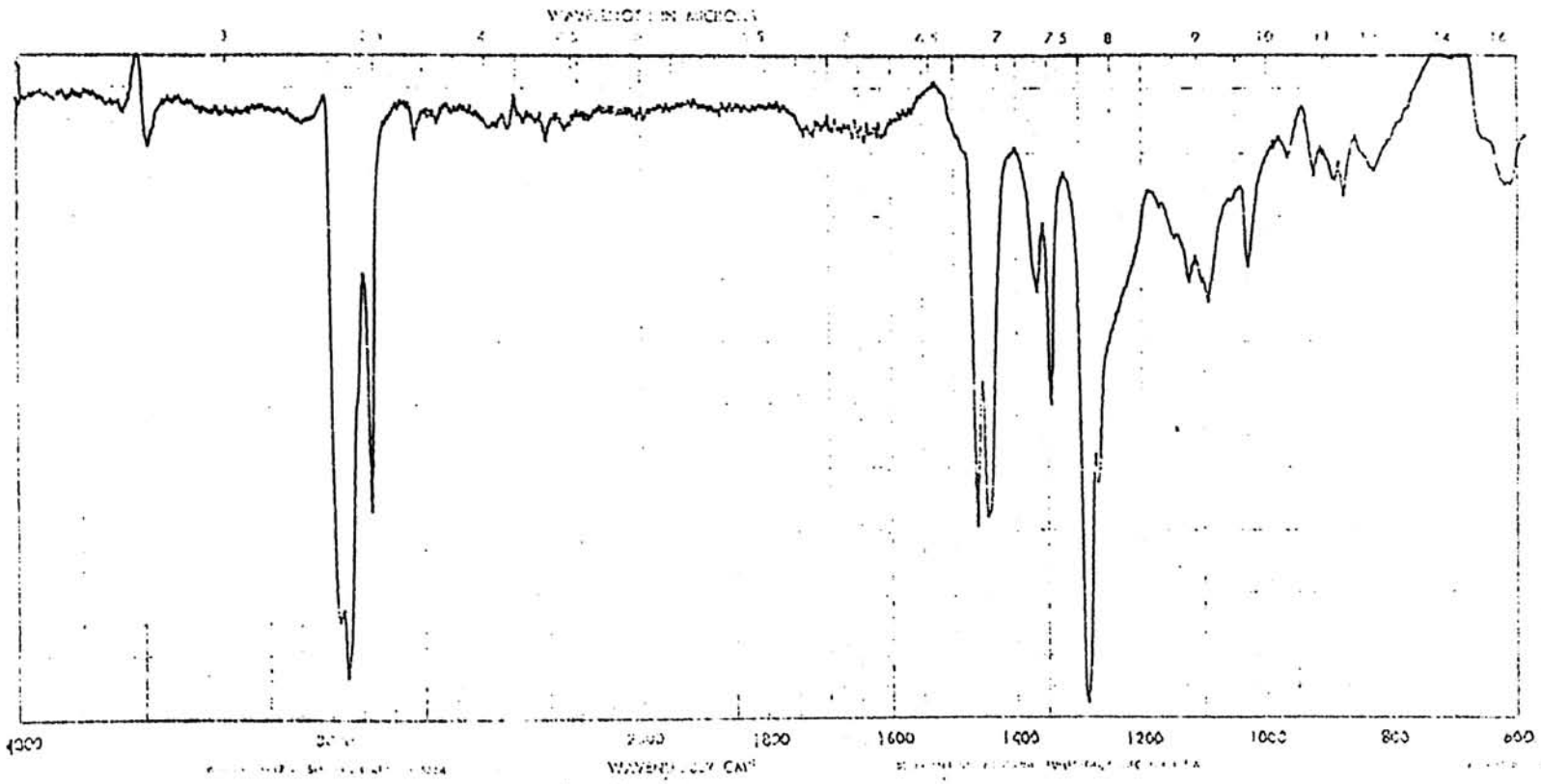

Fig. 54. IR Spectrum of Component A. (2% in $CHCl_3$).

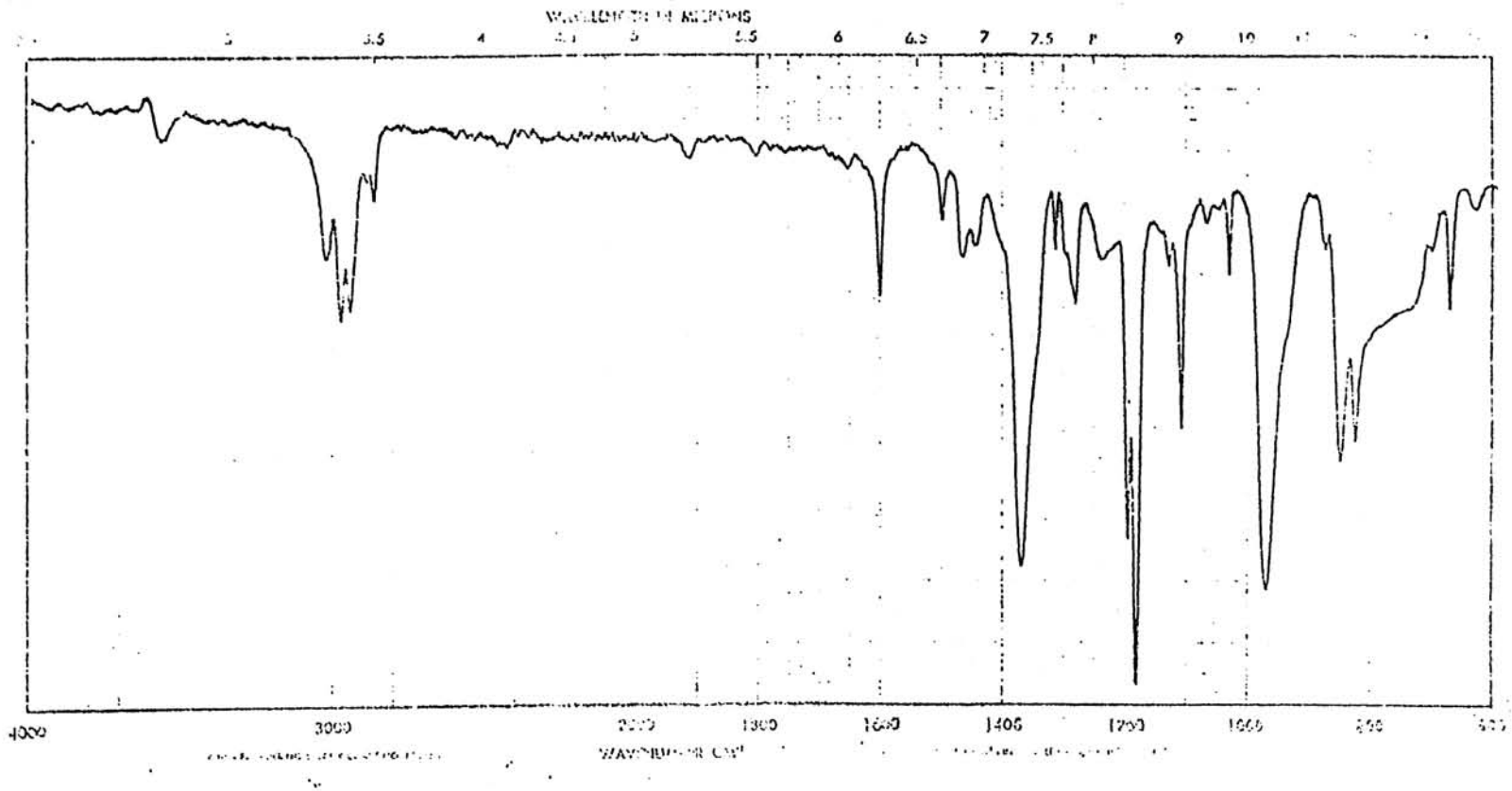

Fig. 55. IR Spectrum of Component B. (1% in $CHCl_3$)

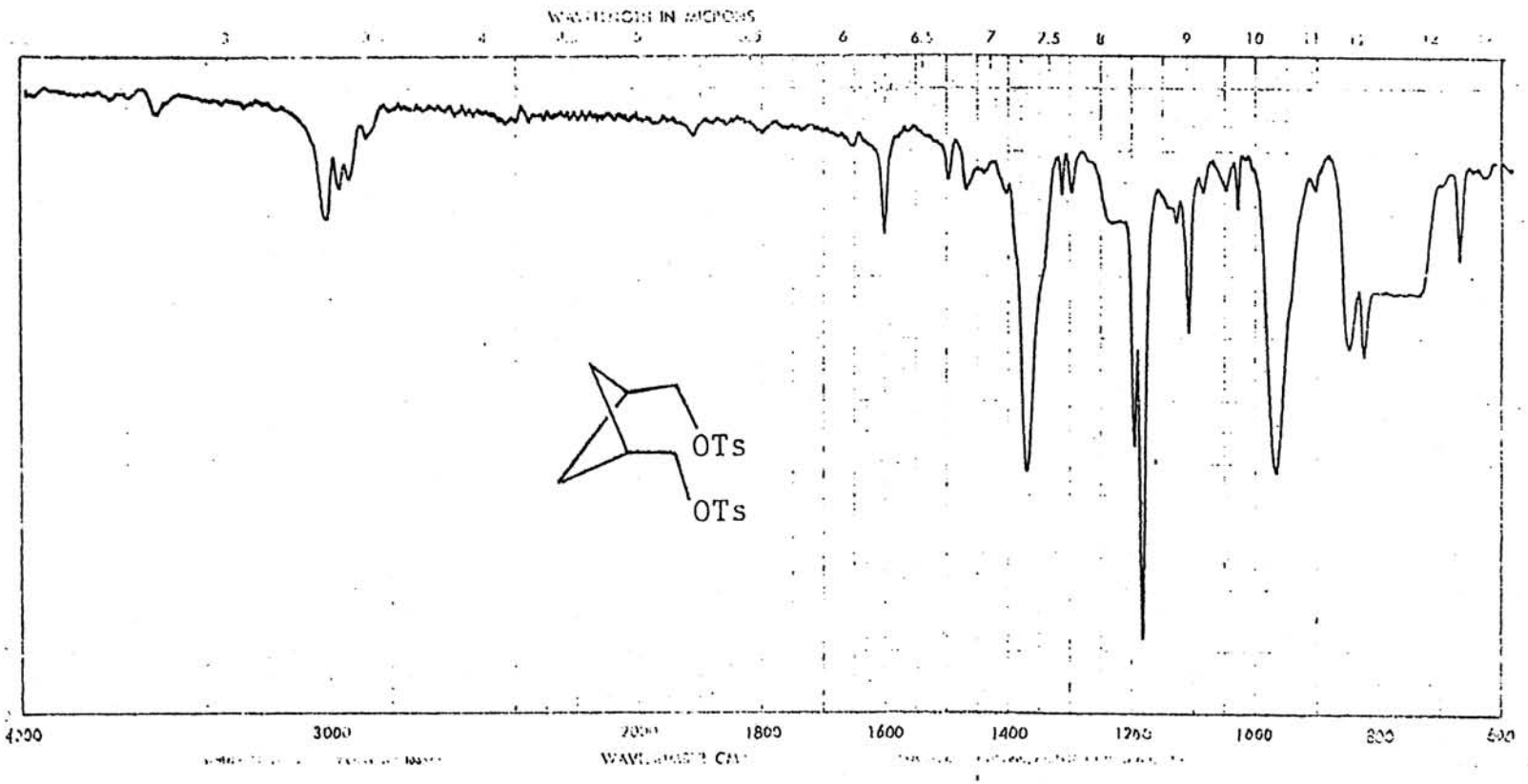

Fig. 56. IR Spectrum of the Ditosylate of cis-1,3-Bis(hydroxymethyl)cyclobutane (120a). (1% in $CHCl_3$).

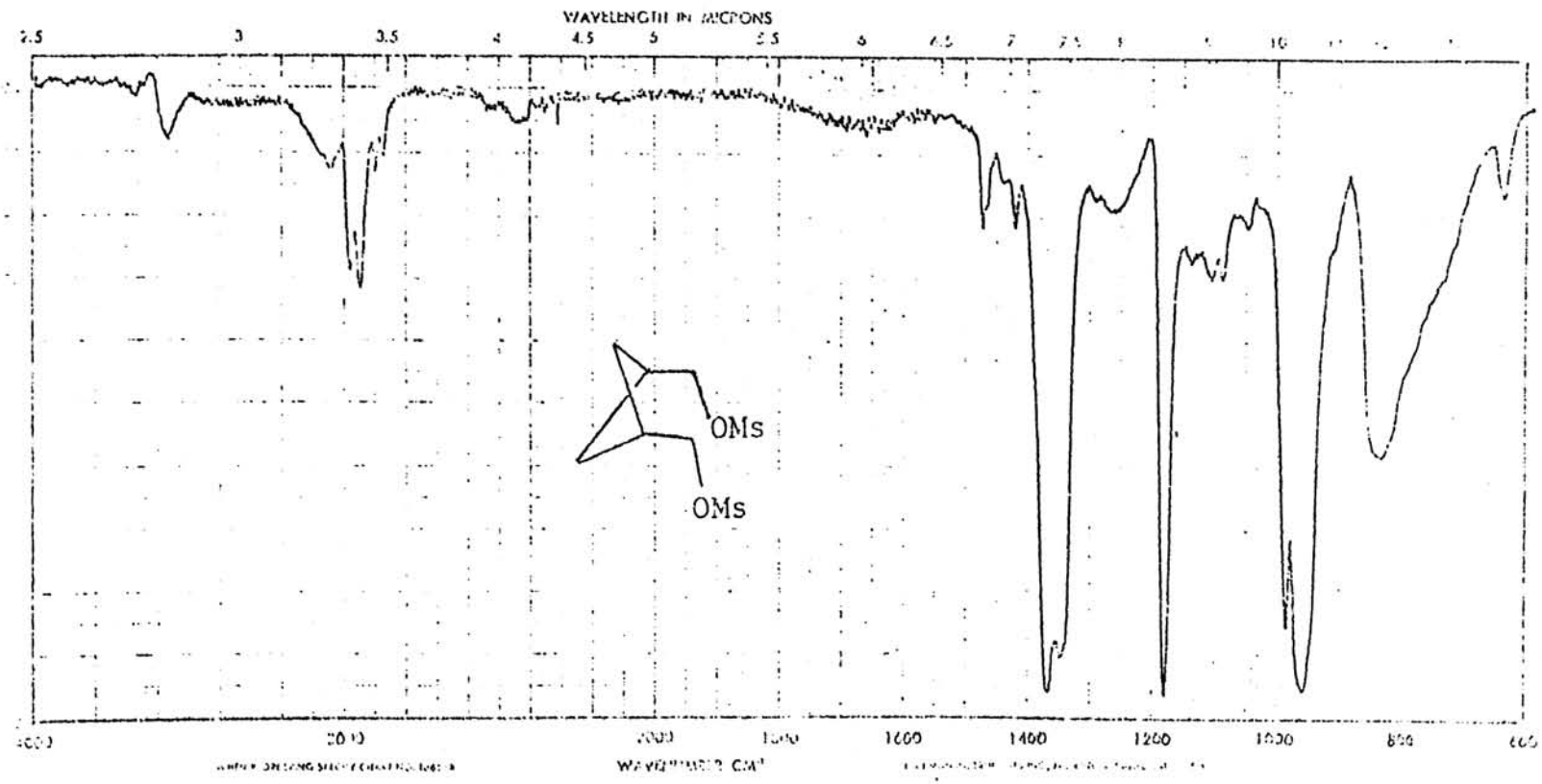

Fig. 57. IR Spectrum of the Dimesylate of cis-1,3-Bis(hydroxymethyl)cyclobutane (120b). (1% in $CHCl_3$).

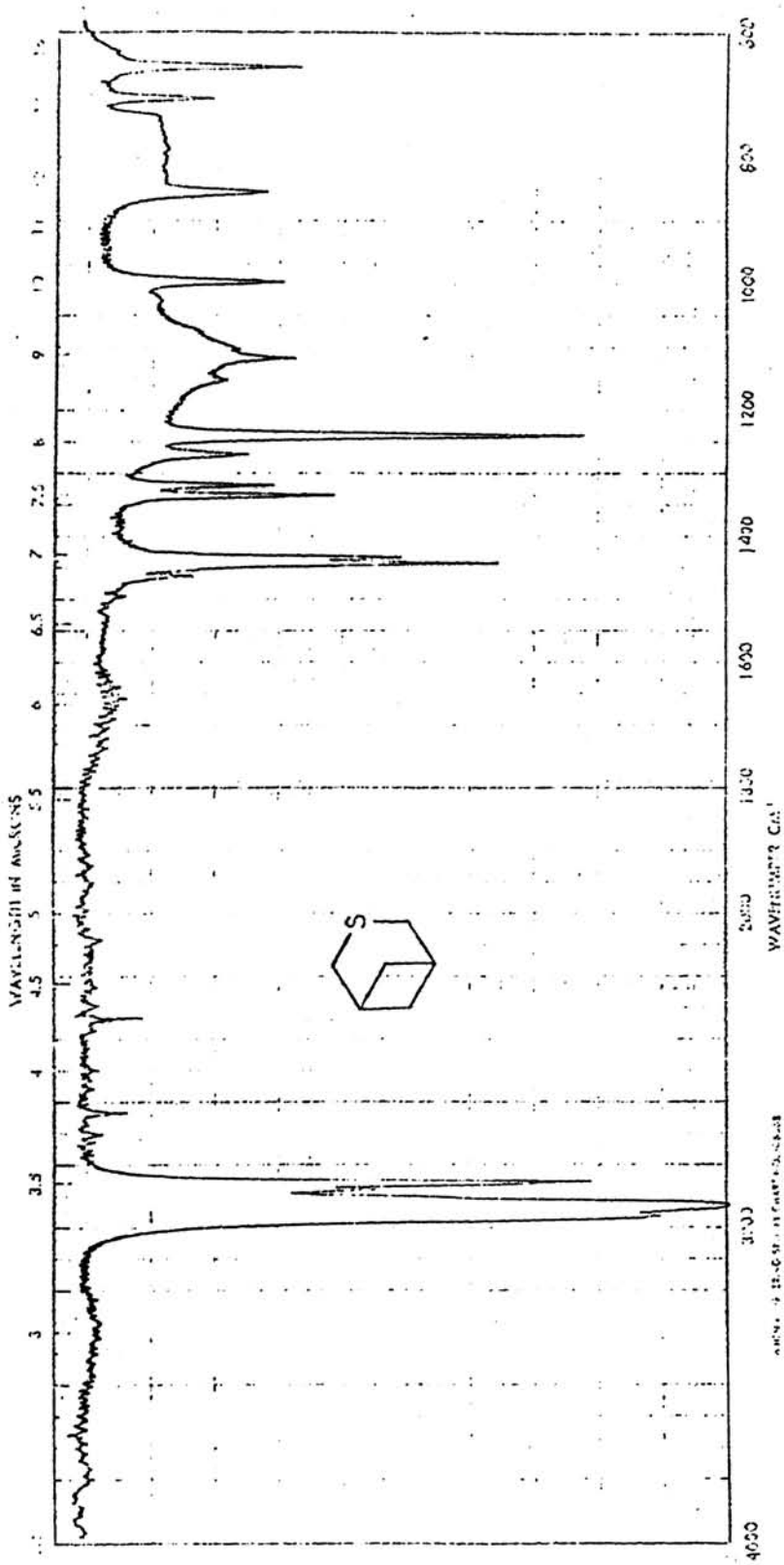

Fig. 58. IR Spectrum of 3-Thiabicyclo[3.1.1]heptane (121). (2% in CCl_4)

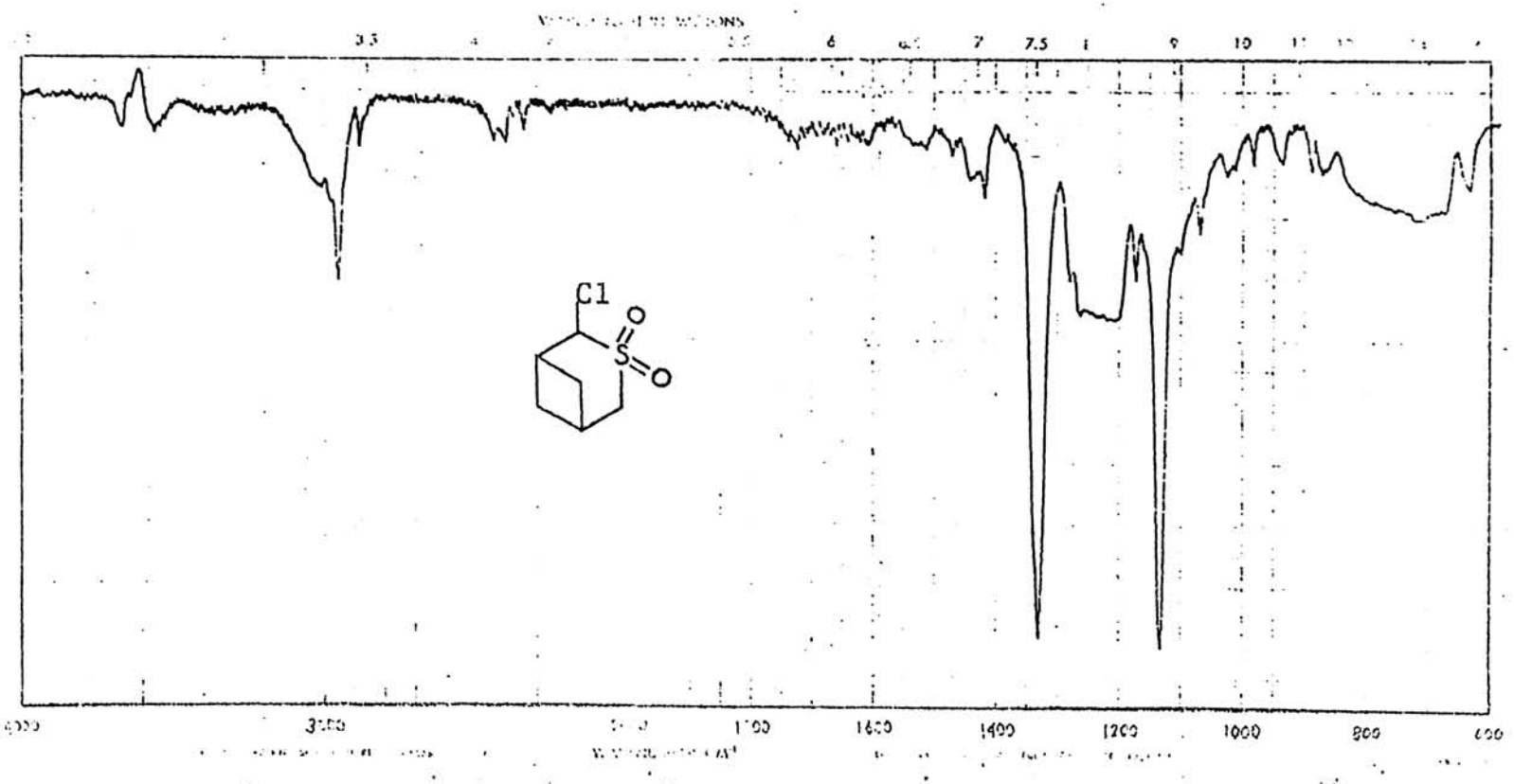

Fig. 59. IR Spectrum of 2-Chloro-3-thiabicyclo[3.1.1]heptane 3,3-Dioxide (122). (1.7% in $CHCl_3$).

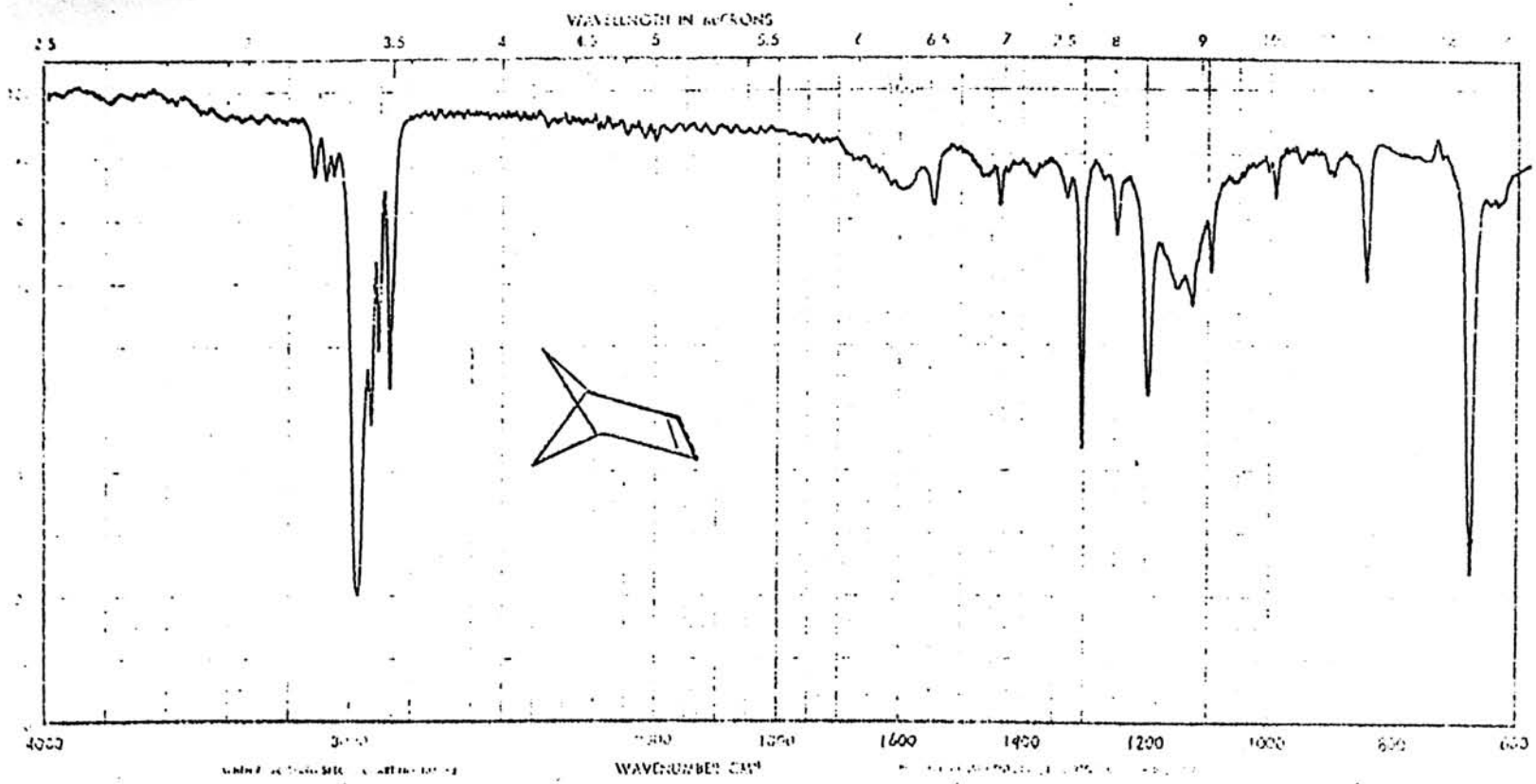

Fig. 60. IR Spectrum of Bicyclo[2.1.1]hex-2-ene (78). (2.7% in CCl_4).

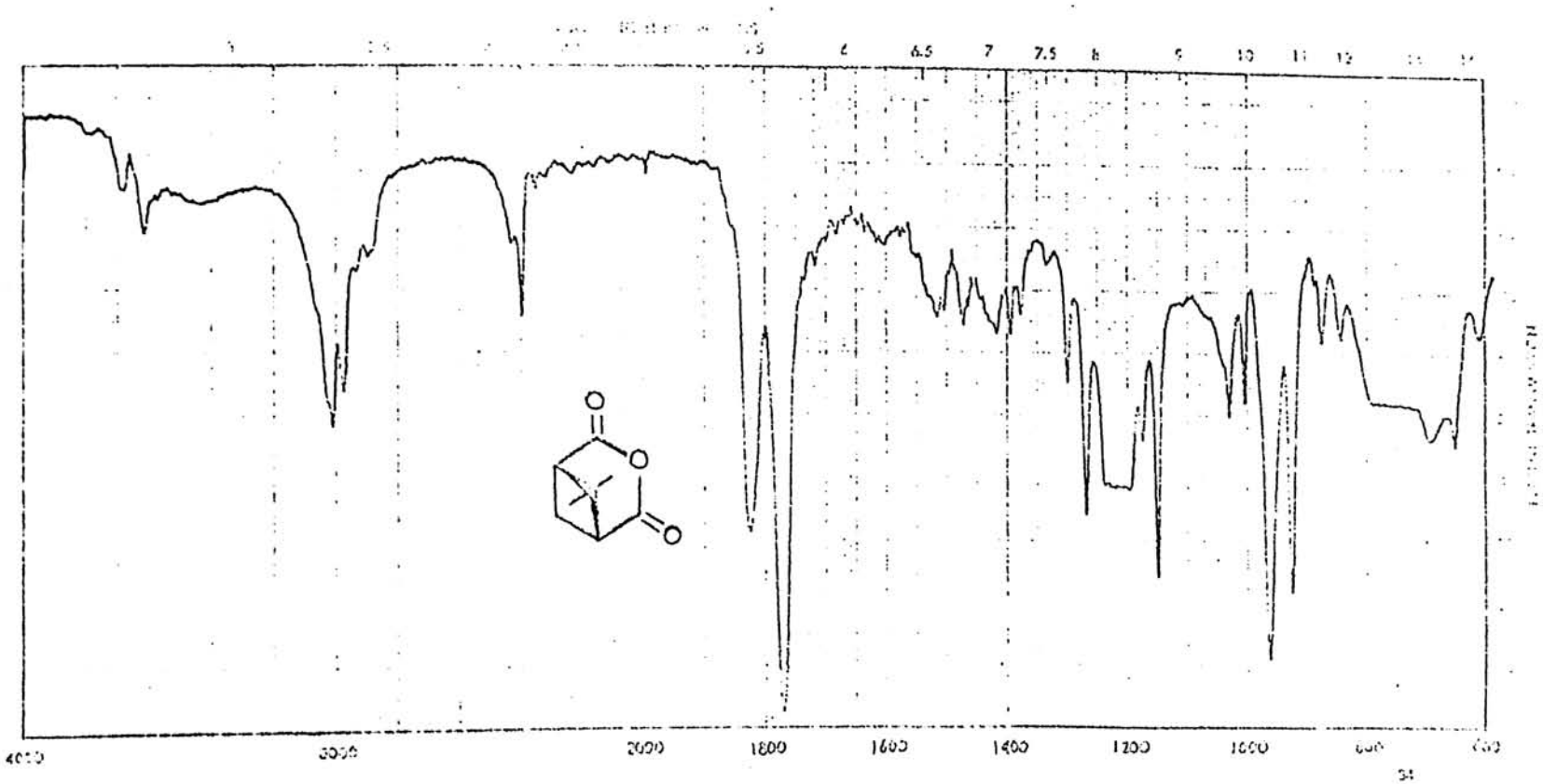

Fig. 61. IR Spectrum of Norpinic Anhydride (129). (1% in $CHCl_3$)

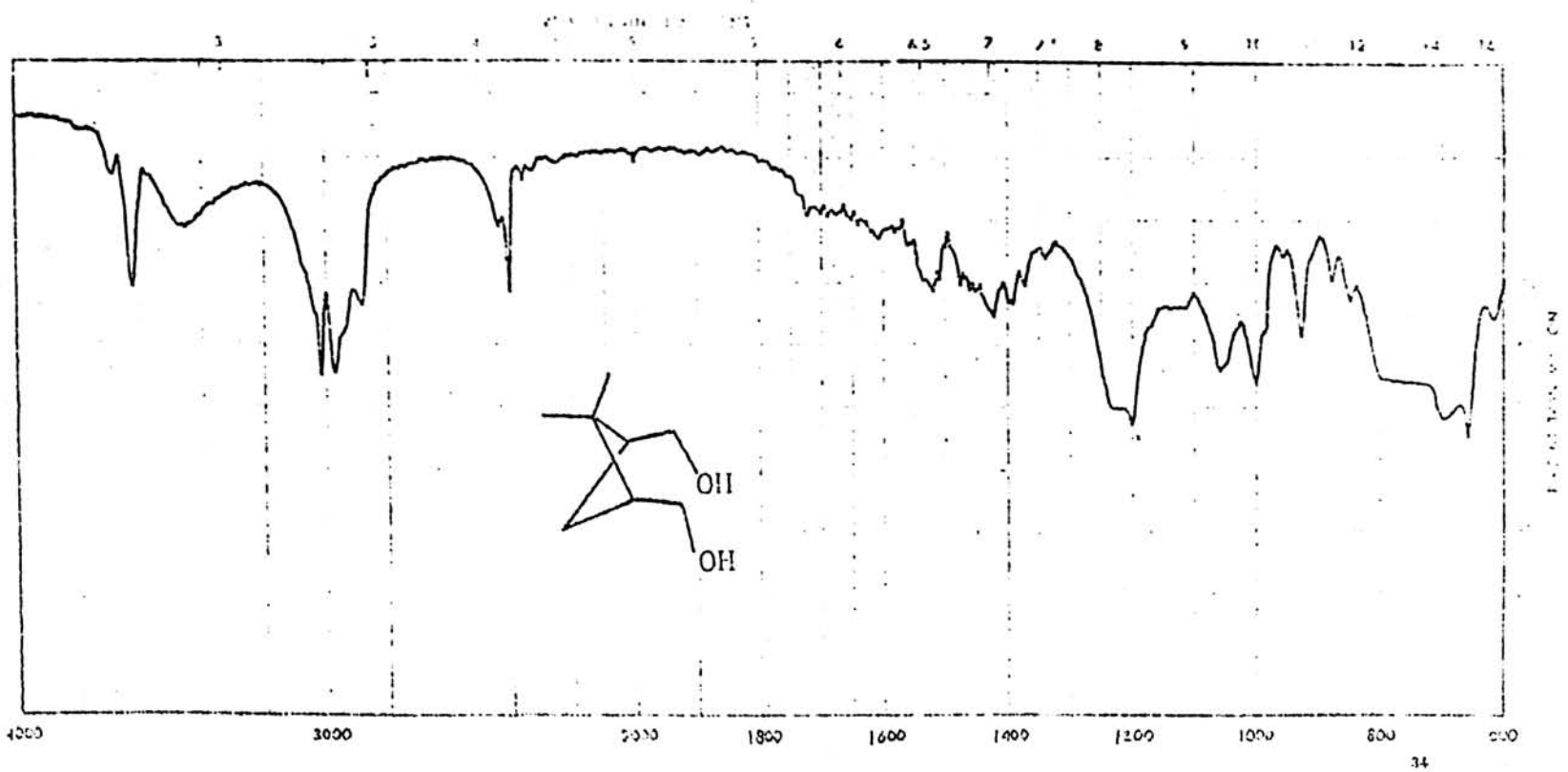

Fig. 62. IR Spectrum of cis-1,3-Bis(hydroxymethyl)-2,2-dimethylcyclobutane (130). (1% in $CHCl_3$).

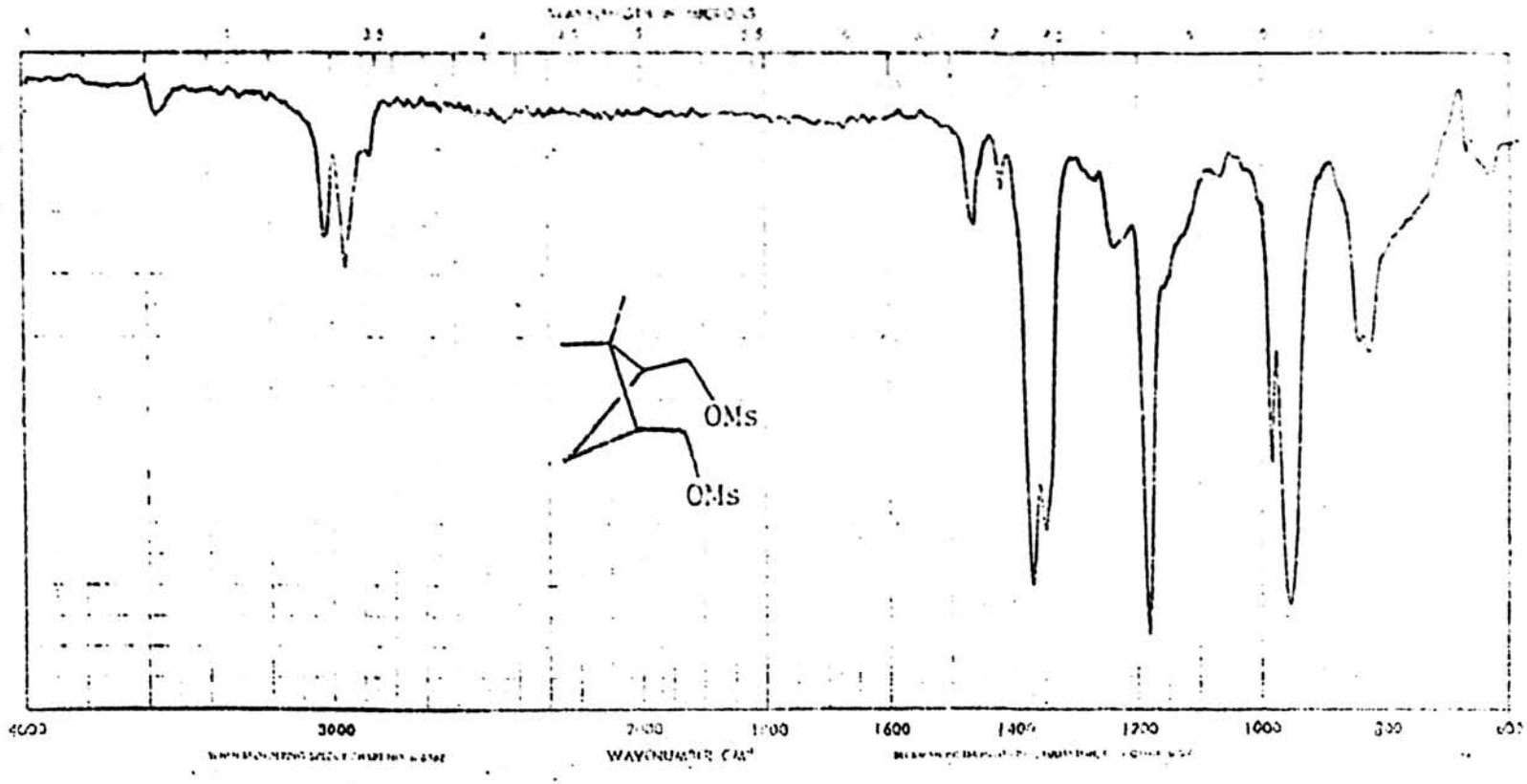

Fig. 63. IR Spectrum of the Dimesylate of cis-1,3-Bis(hydroxymethyl)-2,2-dimethyl-cyclobutane (131). (2% in $CHCl_3$).

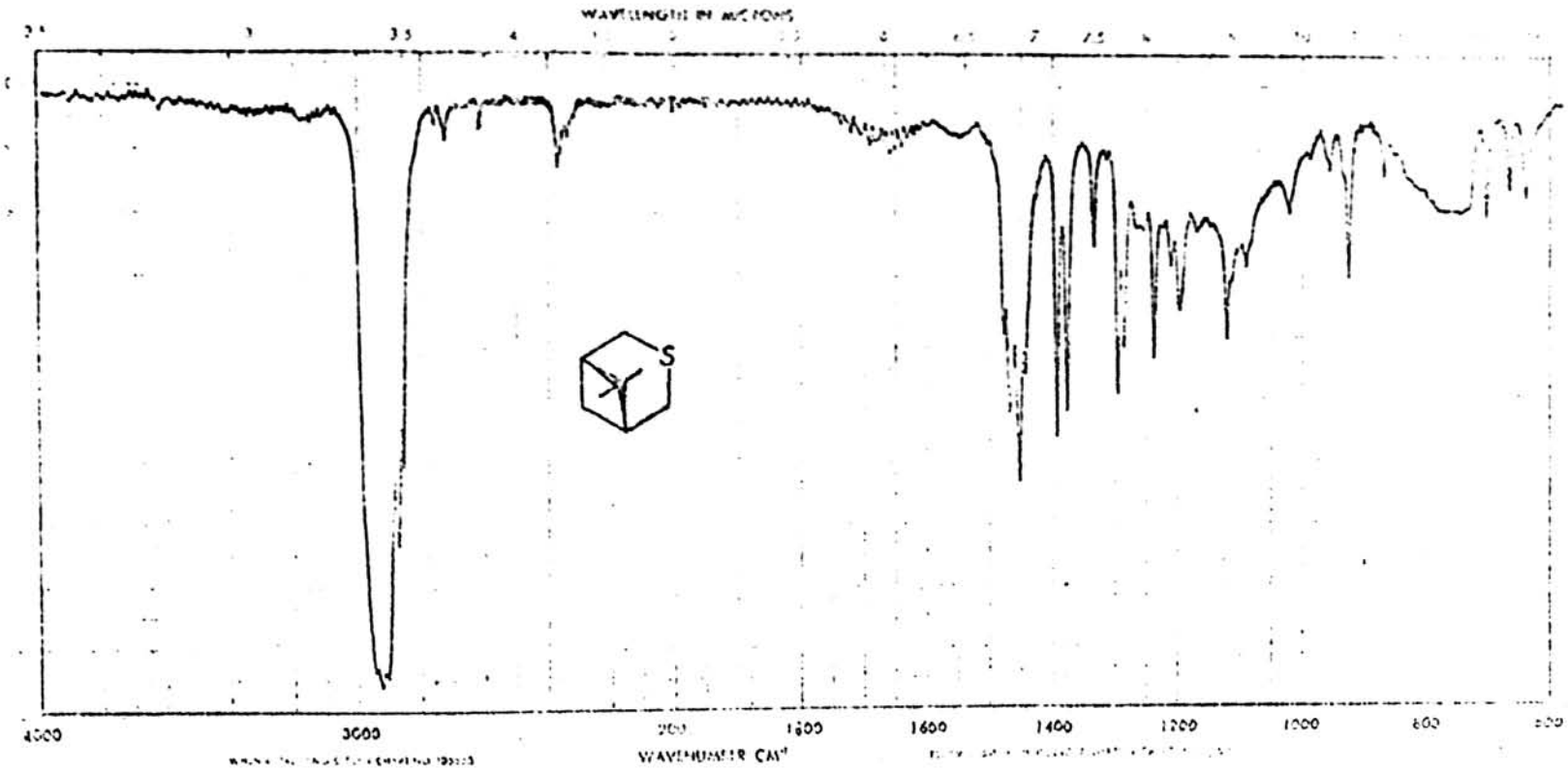

Fig. 64. IR Spectrum of 6,6-Dimethyl-3-thiabicyclo[3.1.1]heptane (132). (2% in CCl_4).

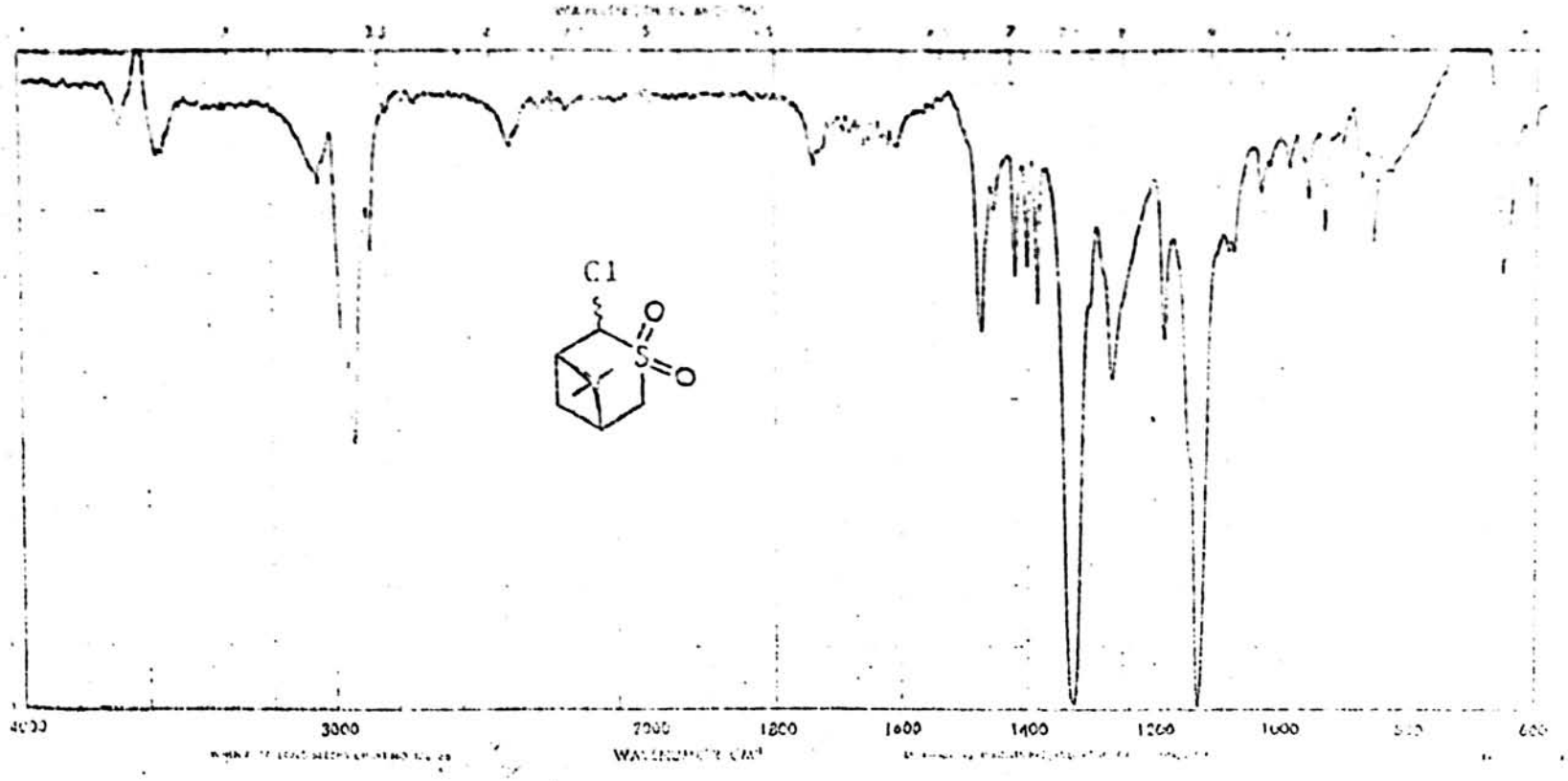

Fig. 65. IR Spectrum of 2-Chloro-6,6-dimethyl-3-thiabicyclo[3.1.1]heptane 3,3-Dioxide (125). (2% in $CHCl_3$).

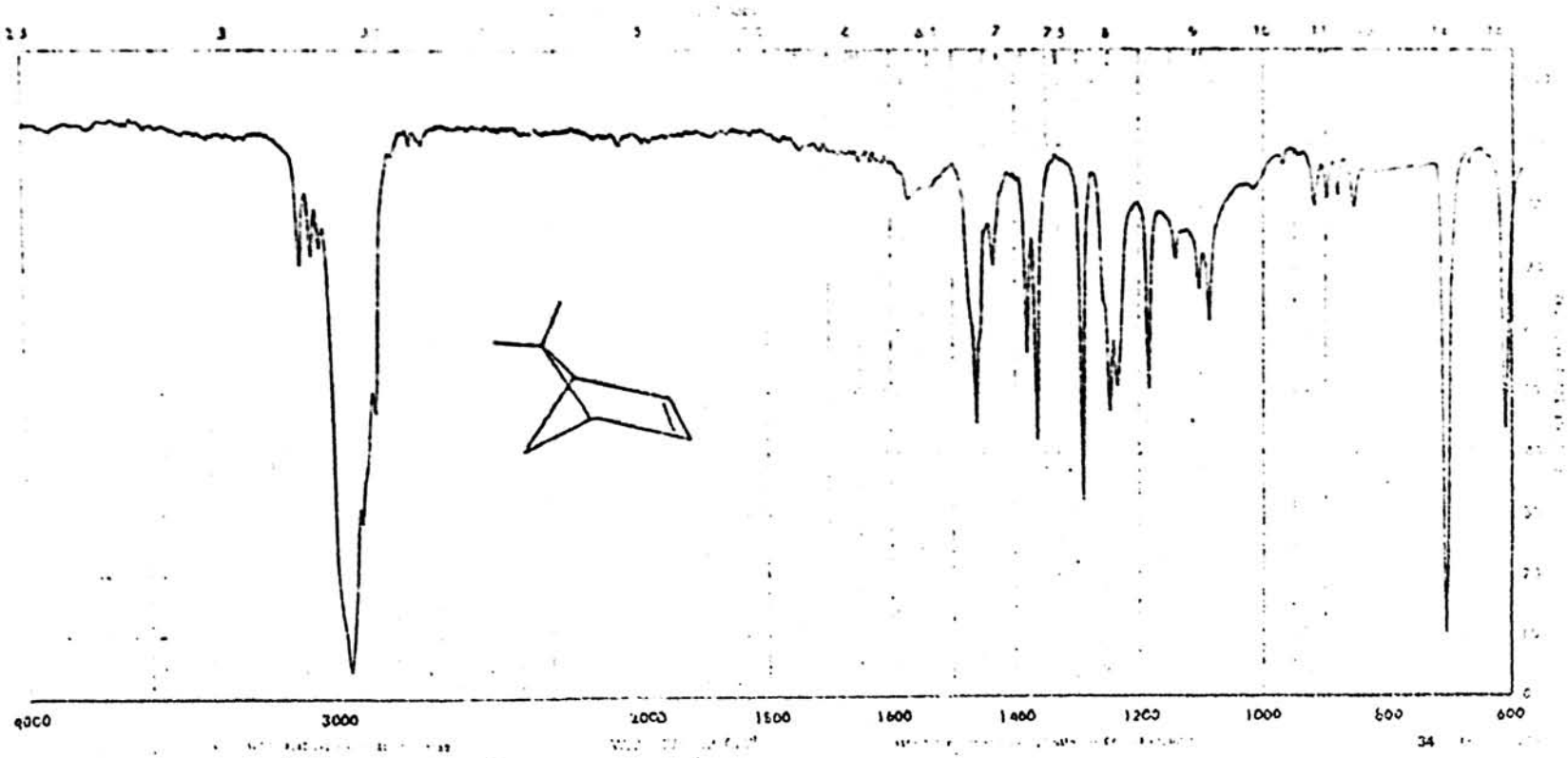

Fig. 66. IR Spectrum of 5,5-Dimethylbicyclo[2.1.1]hex-2-ene (126). (2% in CCl_4)